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Two Dose Versus Five Dose of Sulphadoxine/Pyrimethamine for Malaria Chemo-Prophylaxis in Pregnancy in A Nigerian Sub-Rural Tertiary Hospital: A Randomized Controlled (Open Label) Trial

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Abstract

Malaria has been described as a disease of poverty and under development. It remains a complex and overwhelming health problem, with 300 to 500 million new cases and two to three million deaths per year. Ninety percent of all deaths attributable to malaria occur in Sub-Saharan Africa. Frequency and severity of complication increase during pregnancy as a result of transient depression of cell mediated immunity. The World Health Organization (WHO) currently recommends a package of interventions for controlling malaria during pregnancy in areas with stable transmission of Plasmodium falciparum, which includes the use of insecticide treated nets (ITNs), the administration during pregnancy of at least two doses of intermittent preventive treatment (IPTp) with Suphadoxine- Pyrimethamine combination(S/P) after quickening and 4 (four) weeks later, and effective case management of malaria. Ongoing observational studies monitoring IPTp effectiveness has shown that in areas of high S/P efficacy, 3 doses of S/P were more effective than 2 doses. It has been observed that there is a dose-dependent association of S/P combination with beneficial maternal and fetal outcome with

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more than two doses of S/P. Objective: This study compares the prevalence of placenta malaria parasitaemia on histological assessment in patients using 2 doses and 5 doses of prophylactic Suphadoxine/Pyrimethamine and obstetric outcome.This was a prospective single center two arms randomized controlled (open label) trial in Irrua Specialist Teaching Hospital (ISTH), Irrua from March to November,2015. 278 participants were randomized into two groups A and B (group A receives two doses and group B receives five doses). Data was analyzed with SPSS 16 IBM. Statistical comparison was done using chi- square for categorical variables and multivariate analysis. The level of significance was accepted when P- value is equal to or less than 0.05 and confidence interval of 95%. Primary outcome measure was placenta tissue plasmodium parasitaemia. In this study 278 pregnant women were recruited and randomized into two groups A and B with 20.9 % drop out rate, hence 220 participant were analyzed out of which; 115(52.3%) for group A and 105(47.3%)for group B. There were no differences between monthly (5) S/P doses (n=105) and the standard two doses S/P regimen (n=115) in placenta malaria parasitaemia by histopathology (21.9% vs 26.3% X2= 0.439, P= 0.0508).There were also no differences in the mean values of placenta weight, cord PCV, fetal weight and maternal PCV in labour with placenta parasitaemia. However there was an inverse relationship between placenta parasiteamia with maternal parity, also rural dwellers have more placenta parasiteamia compared to urban dwellers. It has been concluded from study that two dose of Sulphadoxine Pyrimethamine for Intermittent Preventive Treatment is as efficacious as five doses of S/P regimen in prevention of malaria in pregnancy and adverse feto-maternal outcomes. There is need to provide sulphadoxine / pyrimethamine for all pregnant women free in a (unless contraindicated) free in directly observed therapy.

Keywords

Sulphadoxine pyrimethamine, malaria prophylaxis, placenta parasitaemia.

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I. Introduction

Malaria poses a serious public health problem in most tropical and subtropical countries of the world. About 40% of the world's populations in over 100 countries are at risk of malaria infection [1]. Malaria infection during pregnancy remains an important health concern especially in the tropics with substantial risk for the mother, her fetus and the neonate. It's estimated in 2010 that 216 million episodes of malaria occurred worldwide with resultant 655,000 deaths [2]. Up to 91% of malaria burden in that year occurred in Africa. It is an important public health problem globally and especially in Sub-Saharan Africa due to climatic factors, poor environmental sanitation and cultural habits which provide conducive atmosphere that allows transmission of the parasite throughout the year [3].Most studies from Sub-Saharan Africa showed that about 25 million pregnant women are at risk of malaria infection every year while it is estimated that 40% of the world's pregnant women are exposed to malaria infection during pregnancy [4]. In Nigeria, at least 50% of the population have malaria infection annually with under-five children and pregnant women at greater risk of the debilitating effects of the infection [4].

In areas where malaria is highly endemic, a protective semi-immunity against P. falciparum is acquired during the first 10 to 15 years of life, and the majority of Malaria-related morbidity and mortality occur in young children [5].However pregnant women in endemic areas are highly susceptible to malaria, both the frequency and the severity of disease are higher in this group of women [6]. In pregnancy, there is a transient depression of cell-mediated immunity that allows fetal allograft retention but also interferes with resistance to various infectious diseases [7,8].

In sub-Saharan Africa, pregnant women are more likely than their non-pregnant counterparts to become infected with Plasmodium falciparum malariae and have a higher density of parasitemia [9]. In areas of high Plasmodium falciparum transmission, infection in pregnancy is frequently asymptomatic but can lead to parasite sequestration and altered placental intergrity [10].With resultant impairment of fetal nutrition which contributes to low birth weight, which is a leading cause of poor infant survival in Africa [11,12]. Presumably through decreased nutrient transport across the placenta .Additionally, malaria parasitaemia may contribute to maternal anemia, placenta malaria and maternal anaemia can precipitate preterm delivery leading to low birth weight(LBW) [13]. Malaria in pregnant women is an important cause of stillbirths, and low birth weight. In areas with high P. falciparum malaria transmission, women may have substantially acquired anti malaria immunity, however women in their first and second pregnancies are most at risk of malaria [14, 15]. and of malaria-associated low birth weight (LBW).

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World Health Organization recommends that women living in malarious areas should receive chemoprophylaxis during pregnancy, using two doses of sulphadoxine / pyrimethamine at quickening and four weeks later in reducing the frequency of clinical and placental malaria. Recently there is a growing concern over the effectiveness of the 2 dose regimen of S/P for intermittent preventive therapy in areas with high level of resistance to S/P. Some observational studies have shown that 3 or more doses of S/P may be more effective in reducing the incidence of placenta parasiteamia with a better fetal-maternal outcome compare to the current two dose regiment.

To evaluate the prevalence of placental parasiteamia following the use of two doses of S/P and five doses of S/P and to compare the effectiveness of the prophylaxis and obstetrics outcome in the two groups.

As a result of the consequences of P. falciparum infection during pregnancy, the World Health Organization recommends that women living in malaria endemic areas should receive chemoprophylaxis during pregnancy [16]. In 1994, Schultz et al, demonstrated that two treatment doses of S/P, administered once in the second and once in the third trimester, was efficacious in decreasing placental malaria in an area where persons receive, on average, 50 infective mosquito bites per year [17]. Important remaining questions include whether such a two-dose S/P regimen would be sufficiently efficacious in an area with even higher malaria transmission. Studies have shown that intermittent treatment with either monthly dosing or two doses of S/P in the second or third trimester of pregnancy were well tolerated and were effective in reducing the frequency of placental malaria. The review of recent evidence suggests that in sub-Saharan Africa, in spite of the increased prevalence in Plasmodium falciparum of molecular markers associated with resistance to S/P (based on quintuple mutant dhps/dhfr haplotypes prevalence), intermittent preventive treatment with sulphadoxine pyrimethamine (IPTp-SP) remains effective at preventing peripheral parasitemia, maternal anemia, and clinical malaria during pregnancy and is associated with reduced neonatal mortality [18-21]. An ongoing series of facility-based observational studies evaluating IPTp effectiveness in areas with high prevalence of molecular markers of S/P resistance (quintuple mutations) in Kenya, Malawi, Tanzania and Zambia also indicate that IPTp remains safe. Despite the known side effects associated with sulfonamides, S/P for intermittent preventive treatment in pregnancy is generally very well tolerated. Mild and transient side effects including nausea, vomiting, weakness and dizziness have been reported by some women, particularly with the first dose of SP. Studies have demonstrated that side effects tend to decrease with the administration of further doses [22,23]. Side effects should be discussed openly and managed in the antenatal clinic. One observational study in Tanzanian women in an area with high levels of quintuple mutation, and where the parasite dihydropteroate synthase(dhps)resistance mutation of codon

581 was also present, showed increased placental parasite density and placental signs of inflammation in women reporting use of IPTp-SP shortly before delivery [24]. These findings have not been confirmed in other studies and need further investigation [25, 26]. There is limited evidence of potential teratogenicity when S/P is used in the first trimester [27,28]. Thus, until more safety data becomes available, the drug should not be used during the first trimester. During these early weeks of pregnancy, a woman should protect herself against malaria by using an insecticide-treated net. Previously, there was concern that the administration of S/P late in pregnancy could result in kernicterus. However, review of the evidence suggests that there is no clinical association between S/P use and kernicterus, despite the extensive use of S/P and related compounds to prevent maternal malaria and treat congenital toxoplasmosis in near-term pregnant women and newborns.

` However sulpadoxine/pyrimethamine (S/P) is a Sulpha containing drug and should be avoided in women with Glucose-6-phosphate dehydrogenase (G6PD) deficiency. It can precipitate acute haemolytic crisis, neonatal jaundice and kernicterus Prevalence of G6PD deficiency is not known in Irrua but cases has been reported in ISTH, Irrua. Information on the prevalence of G6PD deficiency is fragmented in sub-Saharan Africa, prevalence figures have been generated using different methods so that it is difficult to compare and summarize the available information [29,30]. Although it is considered the most common enzyme deficiency affecting about 5% of the world population [31].

Various data suggest a generally beneficial dose dependent effect of S/P on maternal and neonatal outcomes when administered on one (1),two(2) or three(3) doses .The number of IPTp doses that need to be administered during pregnancy to achieve the maximal beneficial effects of IPTp was examined in the unpublished meta-analysis by Kayentao et al. The meta- analysis, which included seven controlled trials conducted in five Sub-Saharan countries from 1994 to 2008, showed that three (3) or more doses (median of four doses) of IPTp with S/P was superior to the standard two (2) dose regimen in preventing Low Birth Weight (LBW) rates (relative risk reduction of 21% [95% CI 8-32]) both in HIV infected and uninfected pregnant women and in all gravidity groups. Furthermore, women who received a median of four doses of IPTp-SP compared to those on the two dose regimen also had a lower risk of moderate-severe maternal anemia, maternal malaria at delivery, and placental malaria. The meta-analysis, which included two trials in areas of Burkina Faso and Mali where the efficacy of S/P remains high, showed that even in areas of high S/P efficacy, 3 doses were more effective than 2 doses. Ongoing observational studies monitoring IPTp effectiveness in Burkina Faso and Mali also show that even in areas with low levels of S/P resistance, there is a dose-dependent association with beneficial maternal and fetal outcomes.

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(a) SIGNIFICANCE OF STUDY.

Malaria is a known cause of direct and indirect maternal mortality even among pregnant women living in areas of high transmission .It may alter the course of pregnancy by affecting the health of the mother and interrupting the pregnancy. It is associated with maternal, fetal and neonatal complications which include spontaneous abortions, maternal anemia, intrauterine growth restriction, preterm delivery, low birth weight and still birth [32]. Babies born with low birth weight are four times more likely to die as infants than babies born with normal birth weight and at least 13% of all infant deaths can be attributed to low birth weight [33,34]. Malaria also accounts for 8-14% of low birth weight babies [34]. Asymptomatic congenital malaria parasitaemia has also been reported in 8-15% of new born infants [35]. Annual perinatal mortality caused by malaria is estimated to be 25-80/1000 births and each year 75000 – 200000 infant deaths are associated with malaria infection in pregnancy [34].

In areas where P.falciparum malaria is endemic, anaemia is a common feature, especially in young primigravidae. Such patients may show enlargement of the spleen (and sometimes liver).Institution of anti malaria chemoprophylaxis at this early stage will prevent the development of severe degree of anaemia. S/P has proved effective in reducing the level of parasitaemia when given as prophylaxis. Observational studies have shown that the effect of S/P on the prevalence of peripheral and placenta malaria parasitaemia is dose dependent, three or four doses irrespective of the woman's retroviral status may be more effective with a better obstetric outcome, compared to the two dose regimen.

(b) REVIEW OF LITERATURE

BURDEN OF MALARIA IN PREGNANCY

Malaria infection during pregnancy is a major public health problem in tropical and subtropical regions throughout the world.[36] It poses substantial risks to the mother, her fetus and the neonate [37]. In Nigeria, malaria during pregnancy is responsible for 11% of maternal mortality [38]. Forty eight percent of pregnant women were diagnosed with malaria in Nigeria according to the Federal Ministry of Health 2005 [38]. In southwest Nigeria, past studies reported malaria parasite prevalence between 60% and 72% among pregnant women [40]. It also accounts for 40% of public health expenditure, 50% of outpatient visits and 30- 50% of hospital admissions in areas where transmission is high [41]. Pregnant women and their infants are highly vulnerable to malaria. More than 25 million African women in malaria endemic areas get pregnant and are at risk of infection with Plasmodium falciparum. Among pregnant women, studies have shown that the highest prevalence of malaria infection occurs in the second trimester, with infection rate at delivery and in the postnatal period approximating to levels in non-pregnant women [42]. Several pregnancy complications

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like miscarriage; preterm labour, intrauterine growth restriction (IUGR) and intrauterine fetal death (IUFD) have been associated with malaria infection.

The stress of pregnancy tends to lower the immunity acquired in the non-pregnant state leading to increase in frequency and severity of malaria in pregnancies. It has been argued that when protein requirement is unusually high, as in pregnancy, metabolic channels may be altered so that, if dietary intake is insufficient, protein is withdrawn from the immune system. Another explanation is that cortisol levels are increased during pregnancy and this may contribute to decreased cell mediated immunity. As a result of this decline in immunity malaria in pregnancy is more common, more atypical and severe, the mortality is also double (13 %) compared to the non-pregnant population (6.5%) [43]. Complicated malaria such as cerebral malaria is more common in pregnant women in unstable malaria regions with resultant high mortality [44]. Breakdown of malaria immunity is more marked in first pregnancy and thus nulliparous women are more vulnerable to severe malaria and their foetuses similarly show more pronounced adverse effects [43].

PATHOGENESIS OF MALARIA.

Malaria is a mosquito-borne infectious disease caused by parasitic protozoans (a group of single-celled microorganism) belonging to the genus Plasmodium [45]. The disease is transmitted most commonly by an infected female Anopheles mosquito. The mosquito bite introduces the parasites from the mosquito's saliva into a person's blood.[45]The parasites then travel to the liver where they mature and reproduce and the symptoms usually begin ten to fifteen days after being bitten. Five species of Plasmodium can infect and be spread by humans [46]. Most deaths are caused by P. falciparum because P. vivax , P. ovale, and P. malariae generally cause a milder form of malaria [46].The species P.knowlesi rarely causes disease in humans [45]. The disease is widespread in tropical and subtropical regions that are present in a broad band around the equator [46]. This includes much of Sub-Saharan Africa, Asia, and Latin America, Malaria is commonly associated with poverty and has a major negative effect on economic development.

PATHOPHYSIOLOGY Malaria infection develops via two phases, one that involves the liver (exoerythrocytic phase), and one that involves red blood cells, or erythrocytes (erythrocytic phase). When an infected mosquito pierces a person's skin to take a blood meal, sporozoites in the mosquito's saliva enter the bloodstream and migrate to the liver where they infect hepatocytes, multiplying asexually and asymptomatically for a period of 8–30 days [47]. After a potential dormant period in the liver, these organisms differentiate to yield thousands of merozoites, which, following rupture of their host cells, escape into the blood and infect red blood cells to begin the erythrocytic stage of the life cycle [47]. The parasite escapes from the liver undetected by wrapping itself in the cell membrane of the infected host liver cell [48]. Within the red blood cells, the parasites

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multiply further, again asexually, periodically breaking out of their host cells to invade fresh red blood cells. Several such amplification cycles occur. Thus, classical descriptions of waves of fever arise from simultaneous waves of merozoites escaping and infecting red blood cells [47]. Other merozoites develop into immature gametocytes, which are the precursors of male and female gametes. When a fertilized mosquito bites an infected person, gametocytes are taken up with the blood and mature in the mosquito gut. The male and female gametocytes fuse and form an ookinete —a fertilized, motile zygote. Ookinetes develop into new sporozoites that migrate to the insect's salivary glands, ready to infect a new vertebrate host. The sporozoites are injected into the skin, in the saliva, when the mosquito takes a subsequent blood meal [49]. Some P. vivax sporozoites do not immediately develop into exoerythrocytic-phase merozoites, but instead produce hypnozoites that remain dormant for periods ranging from several months (7–10 months is typical) to several years. After a period of dormancy, they reactivate and produce merozoites. Hypnozoites are responsible for long incubation and late relapses in P. vivax infections, although their existence in P. ovale is uncertain [50,51].

SYMPTOMS - The signs and symptoms of malaria typically begin 8–25 days following infection, however, symptoms may occur later in those who have taken antimalarial medications as prevention. Initial manifestations of the disease common to all malaria species—are similar to flu -like symptoms, and can resemble other conditions such as septicemia, gastroenteritis, and viral diseases [52]. The presentation may include headache, fever, shivering, joint pain, vomiting, hemolytic anemia, jaundice, hemoglobin in the urine, retinal damage, and convulsions [53]. The classic symptom of malaria is paroxysm, a cyclical occurrence of sudden coldness followed by shivering and then fever and sweating, occurring every two days (tertian fever) in P. vivax and P. ovale infections, and every three days (quartan fever) for P. malariae. P. falciparum infection can cause recurrent fever every 36–48 hours or less pronounced and almost continuous fever [54]. Severe malaria is usually caused by P. falciparum (often referred to as falciparum malaria). Symptoms of falciparum malaria arise 9–30 days after infection. Individuals with cerebral malaria frequently exhibit neurological symptoms, including abnormal posturing, nystagmus, conjugate gaze palsy (failure of the eyes to turn together in the same direction), opisthotonus, seizures, or coma [55].

COMPLICATIONS-There are several serious complications of malaria. Among these is the development of respiratory distress, which occurs in up to 25% of adults and 40% of children with severe P. falciparum malaria. Possible causes include respiratory compensation of metabolic acidosis, non cardiogenic pulmonary oedema, concomitant pneumonia, and severe anaemia. Renal failure is a feature of blackwater fever, where hemoglobin from lysed red blood cells leaks into the urine [55].

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Infection with P. falciparum may result in cerebral malaria, a form of severe malaria that causes encephalopathy. It is associated with retinal whitening, which may be a useful clinical sign in distinguishing malaria from other causes of fever [56]. Splenomegaly, severe headache, hepatomegaly, hypoglycemia, and heamoglobinuria with renal failure may occur [55]. Complications may also include spontaneous bleeding and coagulopathy. It may cause shock (algid malaria). Malaria in pregnant women is an important cause of stillbirths, infant mortality, abortion and low birth weight, particularly in P. falciparum infection, but also with P. vivax.

PATHOGENESIS OF PLACENTA MALARIA

It is well known that infection with malaria during pregnancy leads to the selective adherence of infected erythrocytes (IEs) in the placenta [57]. Plasmodium falciparum erythrocyte membrane protein 1 (var2csa PfEMP1) is the principal chondroitin sulfate A (CSA) binding ligand mediating placental sequestration of IEs [57,58]. Consequently higher numbers of IEs containing mature trophozoite and schizont stage parasites may be found in the placenta,to higher densities than in the peripheral circulation. Sequestration of parasites in the intervillous spaces (IVS), contributes to maternal morbidity, low birth weight, and preterm delivery [57].

Placenta parasitaemia especially by P. falciparum has been found to be a major contributor to poor obstetric outcome, even among asymptomatic pregnant women with malaria infection [59]. The incidence of placenta malaria parasitaemia at delivery varies between 18.6% and 68%.59The placenta is highly vascularized and thus, it is a favored sight for parasite sequestration and development [57]. Malaria parasites accumulate and multiply within the intervillous spaces of the placenta inducing an inflammatory response resulting in the accumulation of macrophages, elevated levels of tumor necrotic factor, gamma interferon, transforming growth factor, interlukin-2 and alteration in syncytiotrophoblast with reduction in gaseous exchange and nutrient transfer to the fetus [58]. Placenta parasitaemia thus increases the risk of a woman delivering a low birth weight infant due to intra-uterine growth restriction or prematurity [67].

SULPHADOXINE/ PYRIMETHAMINE

MECHANISM OF ACTION: Sulphadoxine and pyrimethamine,(the constituents of Fansidar(R) are folic acid antagonists. Sulphadoxine inhibits the activity of dihydropteroate synthase whereas pyrimethamine inhibits dihydrofolate reductase. In vitro, Sulphadoxine and pyrimethamine are active against the asexual erythrocytic stages of Plasmodium falciparum. Fansidar (R) may also be effective against strains of P. falciparum resistant to chloroquine. Each tablet contains 500 mg N1-(5,6-dimethoxy-4- pyrimidinyl) sulfanilamide (sulfadoxine) and 25 mg 2,4-diamino-5-(p-chlorophenyl)-6- ethylpyrimidine (pyrimethamine). The tablet also contains cornstarch, gelatin, lactose, magnesium stearate and talc.

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STUDIES ON SULPHADOXINE /PYRIMETHAMINE PROPHYLAXIS ON PREGNANT WOMEN.

Malaria infection during pregnancy is a major public health problem, with substantial risks for the mother, her fetus and the neonate. The World Health Organization (WHO) currently recommends a package of interventions for controlling malaria during pregnancy in areas with stable transmission of Plasmodium falciparum, which includes the use of insecticide treated nets (ITNs), the administration during pregnancy of at least 2 doses of intermittent preventive treatment (IPTp) with sulphadoxine- pyrimethamine (SP) after quickening and effective case management of malaria [68].

Studies have been done on malaria prophylaxis in pregnancy, specifically on sulphadoxine/pyrimethamine compared to placenta parasite level at birth, results from the various studies are often discordant, due in part to different techniques of sample collection and analysis in different studies, based on the differences in the definition of placental malaria [69]. Some studies based their definition on the presence of malaria parasite and/or pigments in blood smears from placental blood [69]. Others based their definition on histological findings [70]. No study have compared the two doses of S/P currently recommended by the WHO with five doses and the prevalence of placenta parasitaemia at delivery in a Nigeria rural community like Irrua Specialist Teaching (ISTH).In a study done in South East Nigeria, Adherence to IPT for malaria with S/P and outcome of pregnancy found a higher prevalence of LBW recorded for women who did not receive IPTp compared to those who had three doses. This finding agrees with the findings of Le Hesran et al. although this study did not control for other factors that impact on fetal weight. [71].

Another study done in Ibadan, South western Nigeria (Malaria journal 2007, 6:88) comparing the use of S/P, Pyrimethamine and no Chemoprophylaxis to obstetric outcome shows that at delivery the prevalence of maternal parasitaemia was significantly lower in the group that was administered at least 2 doses of IPT-SP compare to the other groups. Both maternal and placental malaria parasitaemia were also more significant in the group that was not administered IPT- SP. The mean birth weight of babies born to mothers who received S/P was greater than those babies born to mothers in the pyrimethamine and no chemoprophylaxis group. These findings are consistent with other report in East and South Africa countries.

A study done in Kenya to monitor the effectiveness of intermittent preventive treatment (IPT) with sulphadoxine-pyrimethamine (S/P) for the control of malaria in pregnancy at delivery in the Provincial Hospital in Kisumu, Kenya, and to assess the effect of IPT in participants in a cohort study. Between June 1999 and June 2000, information on IPT and birth outcome was collected in 2302 consecutive deliveries. The prevalence of placental malaria was 13.8% and of low birth weight (LBW) was 12.2%. In

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multivariable analysis, IPT (> or =1 dose of SP) was associated with a reduction in placental malaria and LBW [adjusted odds ratio (OR) 0.56, 95% confidence interval (CI) 0.39-0.83 and OR 0.65, 95% CI 0.45-0.95, respectively]. An adjusted mean increase in birth weight of 61 g was seen (95% CI 22- 101 g) for each increment in number of SP doses (> or =2 doses grouped together). IPT was associated with a reduction in placental malaria in HIV sero-negative women (OR 0.49, 95% CI 0.28-0.86) [72].

Preliminary data from recent observational studies have suggested reduced effectiveness of S/P for IPTp in Malawi, the first country where IPTp-SP was implemented in 1993 [72]. In addition, there is growing concern over the decreasing effectiveness of the 2-dose regimen of SP for IPTp in other countries with a high level of resistance to S/P, especially in Eastern and Southern Africa, regions that also carry the highest incidence of HIV in the world [73]. Although some report suggest that monthly IPTp-SP may be more appropriate in areas that are hyper-and holoendemic for malaria. The new policy recommends that SP should be given at each scheduled ANC visit except during the first trimester, and it can be repeated every month with the doses given at least one month apart until the time of delivery. The previous WHO policy recommendation proposed that IPTp-SP be delivered at each ANC visit in order to ensure that pregnant women receive at least two doses of SP. However, this resulted in many countries adopting a policy that recommended the administration of SP only twice during pregnancy. The new WHO policy recommendation calls for the administration of IPTp-SP at each ANC visit, starting as early as possible during the second trimester. This recommendation reflects the need to increase in the number of S/P doses. This decision was based on the most recent evidence that among pregnant women in sub-Saharan Africa, intermittent preventive treatment in pregnancy with more than three doses of S/P was associated with a higher birth weight and lower risk of LBW than compared to the standard two-dose regimens [75]. The new policy does not refer to a specific number of doses, as experience has shown that once the policy states a specific number of doses, even if more effective (e.g. “minimum of 3 doses,” “3 or more doses,” or “at least 3 doses”), this becomes a problematic target for many countries. It is pertinent to state that most studies in sub-Saharan Africa comparing multiple doses of sulphadoxine/pyrimethamine to the prevalence of placenta parasitaemia levels relied on the results of the placental smear, the sensitivity of which is low compared with placental histopathology. Using a more reliable method of assessing placental infection, such as the histological examination, might have given a more accurate result [76].

In some of these studies SP was not administered as direct observed therapy (DOT),four doses may have been recorded for a parturient while in reality she took one or two doses ,due to the common belief by patients that drug should not be taken on empty stomach. In some studies symptomatic

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patients were not separated from patients on prophylaxis, while in others HIV positive pregnant women were included without adjusting S/P prophylaxis to their HIV status. During the last few years, WHO has observed a slowing of efforts to scale-up IPTp-SP in a number of countries in Africa. Although there may be several reasons for this, an important factor is confusion among health workers about sulphadoxine-pyrimethamine administration for intermittent preventive treatment in pregnancy. All this drawback invariably affect the outcome of comparing greater than two doses of SP prophylaxis to placenta parasitaemia at birth.

RESEARCH QUESTION

Is there any ideal dose of sulphadoxine pyrimethamine for malaria chemoprophylaxis in pregnancy?

OBJECTIVE AND WORKING HYPOTHESIS

General objective.

Comparing two dose versus five dose of sulphadoxine/ pyrimethamine prophylaxis and the prevalence of placenta parasitaemia level at delivery.

Specific objectives

1. To determine the effectiveness of two doses versus five doses of sulphadoxine/ pyrimethamine in reducing the prevalence of placenta parasitaemia level at delivery.
2. To evaluate and compare specific obstetric outcome between two doses versus five doses of sulphadoxine pyrimethamine.

Working hypothesis.

Five doses of sulphadoxine/ pyrimethamine prophylaxis is more effective than 2 doses of S/P in reducing placenta parasitaemia at delivery and improving obstetric outcome.

Null Hypothesis (Ho)

Five doses of sulphadoxine/pyrimethamine prophylaxis is not effective compared to two doses in reducing placenta parasitaemia at delivery and in improving the obstetric outcomes.

II. Material and Methods

Study setting

The study was conducted in the ante-natal clinic, labour ward and pathology department of Irrua Specialist Teaching Hospital, Irrua, Edo State, South- South, Nigeria. This hospital serves as a major referral centre for part of Edo, Ondo, Delta and Kogi States. It is located in Irrua, Esan Central Local Government area of Edo state. It serves a population of about 2million persons. Patients are usually referred from General Hospitals, government owned health centres, private medical centres and from other departments in the hospital. The hospital has 22 gynaecological and 32 obstetric beds and undertakes an average of 1,800 deliveries annually.

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STUDY DESIGN

It was a prospective two arms randomized controlled (open label) trial.

STUDY POPULATION

Participants were antenatal attendees of ISTH, Irrua at gestational age of 16 weeks and above.

SELECTION CRITERIA

Inclusion criteria.

This includes all pregnant women who book for antenatal care and deliver in this hospital.

Exclusion criteria.

Retroviral disease positive women.

Pregnant women who have history of allergy to sulphonamide.

Women with previous history of preterm birth

SAMPLE SIZE

The sample size was calculated using the statistical formula [79].

$$n = \frac{2p1\,(1 - P1)\,(Z\beta/2 + Z\beta)\,2}{(P1 - P2)2}$$

n = Desired minimum sample size for comparing proportion in two independent groups or population

P1 = proportion in population 1

P2 = proportion in population 2

p1 = (P1 + P2)/2

Zβ /2 = Standard normal deviate set in this study set at a confidence limit of 95% = 1.96.

Zβ = Standard normal deviate at a confidence limit of 80% = 0.84

In this study

P1= 24.5%.[77] = 0.245

P2 = 11%.[78] = 0.11

p1 =(P1 + P2)/2 = 0.1775

Thus

$$\frac{2 \times 0.1775(1-0.1775)\,(1.96 + 0.84)2}{(0.245-0.11)2} = 125.7$$

n = approx 126

plus 10% attrition = 138.6 approx 139

139 women received two doses of S/P, and another 139 women received five doses of S/P at monthly interval.

SAMPLING TECHNIQUE / RANDOMIZATION

All pregnant women who consented to the study were randomized into two groups - A and B using a simple ballot technique. Group A received the standard 2 doses of S/P and Group B received five doses monthly after quickening. The drug was taken after quickening and under direct observe therapy (DOT). The Two hundred and seventy eight opaque square papers were used. This was divided into two equal groups A and B. All the papers were mixed thoroughly in a ballot box before selection by the participating patient. Each study participant picked up one sealed paper from the bag and gave it to the researcher to open. Afterwards patient was allocated her group and this was boldly noted on her antenatal case record. Sulphadoxine/ Pyrimethamine was obtained from the hospital pharmacy department.

In an attempt to avoid bias, the laboratory scientist, histopathologist were blinded using coded number to label the samples.

STUDY INSTRUMENTS

Structured interviewer questionnaire consisting of five sections was administered to the participants.

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Section A involved documentation of their bio-data and socio- demographic characteristics.

Section B was on information concerning awareness of malaria preventive measures, history of previous malaria chemoprophylaxis and birth weight in previous pregnancies

Section C concern information on index pregnancy, booking parameters, GA at which S/P was first administered and the number of doses administered was noted and if the participant received treatment for malaria was also ascertained

Section D was a proforma for the documentation of the presence and degree of placenta parasitaemia on histological examination.

Section E involved documentation on the feto-maternal outcome, maternal packed cell volume in labour with,fetal weight with placenta parasitaemia, fetal cord PCV with placenta parasitamia ,placenta weight with parasitaemia, preterm delivery, still birth,low birth weight (LBW) and intra uterine growth restrictions (IUGR).

Before the commencement of the study, the questionnaire was pretested on 15 women who came for their routine antenatal clinic to validate it; these women were not included in the final pool of women used for the study.

COLLECTION OF BLOOD SAMPLE

Maternal blood sample was collected into EDTA bottle for packed cell volume(PCV) estimation while in labour. Fetal cord blood was also taken in to EDTA bottle for PCV estimation and send to the haemathologist. Neonate was weighed with a digital weighing scale. Placenta was examined and weighed too with a digital scale. Placenta sample was taken on the maternal surface, placed in a 10% neutral buffered formalin container for histological assessment for malaria parasite.

HISTOLOGICAL EXAMINATION OF PLACENTA TISSUE FOR MALARIA PARASITE: Having acquire the requisite training from the histopathologist who participated in the study (the training was for 2 weeks, our ability to identify malaria parasite within intervillous cells correctly were used as an index of assessing our competence). we examined the placenta with 2 consultant pathologists. Three stains were used Haematoxylin, Eosin and Giemsa. Placenta tissue was stained with Heamatoxylin for 5min, with 1% Eosin for 3min, the tissue was dehydrated in ascending grade of alcohol, then stain with Giemsa for 10min, clear in Xylene and mount with DPX. Placenta histology result was graded according to Bulmer`s description and which was previously used by Adebami et al 2007.[81] as follows:

Grade 0= No evidence of malaria parasite or pigment.

Grade 1(active infection) parasite and pigments in maternal red blood cells in the intervillous space but no pigment in fibrin or cell within fibrin;

Grade 2 (active – on- past infections), parasite and pigments in maternal red blood cell and pigments in fibrin or cell within fibrin;

Grade 3(past infection),parasite not present but pigments confined to fibrin or cells within fibrin.

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COLLECTION METHODS

When the participant present in labour ward, maternal blood sample was taken for PCV estimation within 30min of arrival (2ml in EDTA bottle). After delivery two milliliters of cord blood was collected in a separate EDTA bottle for neonatal packed cell volume estimation, the neonate was weighed with a digital scale at birth. A biopsy specimen of placental tissue (2 by 2 by 1 cm) was excised from the maternal surface of the placenta, this was then placed in 10% neutral buffered formalin in a container and sent for histological examination for malaria parasite within 30 min of collection. The participants were not responsible for the cost of the investigations.

OUTCOME MEASURES

PRIMARY OUTCOME MEASURE

Grade of placenta malaria parasitaemia

Cord blood packed cell volume

Maternal packed cell volume

Secondary outcome measures

Low birth weight

Maternal anaemia

Intra uterine growth restrictions

Preterm birth.

DATA MANAGEMENT

Data was analyzed using SPSS 16 statistical package. Chi-square analysis was used for comparing proportions of categorical variables and multivariate analysis was done .P-value less than or equal to 0.05 were taken as being significant

ETHICAL CONSIDERATIONS

Approval for this study was obtained from the ethical committee of the Irrua Specialist Teaching Hospital. Ethical considerations in this study were based on the general ethical principles as applicable to human subjects. These are respect for persons, beneficence, non-malficience and justice. Adequate information was provided to participant and written consent obtained. They were not coerced or induced to participate and their right to participate or to withdraw from the study were respected.

STUDY LIMITATIONS

It was difficult to completely eradicate bias in the evaluation of the tests result. Such biases were controlled by inclusion of subjects from the general population of pregnant women who came for booking in Irrua specialist teaching hospital and excluding those with conditions that may mimic clinical picture of malaria, secondly; samples were not interpreted concurrently rather they were done in batches. Samples were coded such that the individuals involved in the sample interpretation were not aware of the source of the sample or its association with any patient. Most of the women who had febrile illness in pregnancy were assumed to have had malaria when other causes of fever like urinary tract infection and respiratory tract infection were also possible, to reduce the impact of the assumptions ;women that had fever in the course of the antenatal care had malaria parasite test (MP)done before receiving treatment .

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III. Results

A total of two hundred and seventy eight (278) pregnant women were recruited for this study and randomised into two groups A and B, with each group having 139 participants each. Group A received 2 doses of S/P while group B received 5 doses of S/P.

In Group A, 12 women received treatment for malaria, 7 had preterm delivery while 5 delivered outside the hospital, they were excluded from the study making the total number in group A to be 115(drop-out rate in group A was 17.3%).

In Group B, 8 women received treatment for malaria, 14 delivered outside hospital 10 had preterm delivery and 2 participants opted out of the study making the total number in Group B to be 105 (drop-out rate in group B was 24.5%). The total of 220 women were finally analysed out of which 115(52.3%) were in group A and 105(47.3%) in group B. Age group 26- 31 years had the highest number of participants in both groups; 43.5% and 40.0% in group A and group B respectively. In contrast age group 14-19 years had the lowest number of participants in both groups i.e. 2.6% and 1.9% in group A and group B respectively(P>0.05).

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Majority of the participants that had 2 doses were para 1-4(60.9%). Similarly most of the participants that had 5 doses also were para 1-4 (56.2%). In contrast only 15.6% of those that had 2 doses were ≥ para 5 (7.8%) while about a quarter of those that had 5 doses were ≥ para 5 (24.8%) ($P > 0.05$). Thus this association between the parity of the participants and the doses of S/P given is not statistically significant.

Almost all the participants are married i.e., 98.3% and 100 percent in groups A &B respectively ($P > 0.05$). Thus this association between the marital status of the participants and the doses of S/P given is not statistically significant.

Higher proportion of the participants that took two doses (42.6%) was on skilled level 3. While about half of those that had 5 doses 50 participants were on skilled level 2.($P > 0.05$,)Thus this association between the occupational level of the participants and the doses of S/P given is not statistically significant.

Higher proportion of the participants that took 2 doses of S/P (41.7%) had primary level of education while higher proportion of the participants that took 5 doses of S/P (29.5%) had primary level of education. ($P < 0.05$). Thus this association between the level of education of the participants and the doses of S/P given is statistically significant.

About half proportion of the participants husband that took two doses are skill level4 (44.3%) and (44.7%) in group A and B respectively. Skill level 3 is the next in participants (30.4%) and (41.9%) in group A and B respectively. Skill level 0 is the lowest in participants (4.4%) and (3.8%) in group A and B respectively. ($P > 0.05$). Thus the association between the skilled level of the participant's husbands and the doses of S/P given is not statistically significant.

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About half proportion of the participant's husband that took two doses had primary level of education while similar proportion of those that had 5 doses had primary and secondary levels of education. (P > 0.05). Thus this association between the level of education of the participant's husband and the doses of S/P given is not statistically significant.

Majority of the participants are from rural setting; 66.1% and 78.3% in group A and group B respectively. (P > 0.05). Thus this association between the region of the participants and the doses of S/P given is not statistically significant.

Majority of the participants 69.6% and 84.8% in group A and group B respectively were aware that malaria complicates pregnancy. (P > 0.05). Thus this association between the awareness of the participants that malaria complicates pregnancy and the doses of S/P given is not statistically significant.

Majority of the participants 76.5% and 60% in group A and group B respectively were aware that chemoprophylaxis for malaria prevents malaria complications in pregnancy. (P > 0.05). Thus this association between the awareness of the participants that chemoprophylaxis for malaria prevents malaria complications in pregnancy and the doses of S/P given is statistically not significant.

Most of the participants with previous deliveries, 69.9% and 70.0% in group A and group B respectively had malaria chemoprophylaxis in their previous pregnancy. (P > 0.05)Thus this association between the use of malaria chemoprophylaxis in their previous pregnancy and the doses of S/P given is not statistically significant. The non use of chemoprophylaxis may be due to the fact that antenatal care was supervised in a maternal home or by traditional birth attendance. About half proportion of the participants (49.5%) had a previous birth weight of > 3kg in Group A. While about one quarter of the participants with 5 doses couldn't remember their previous baby's birth weight in Group B. Thus this association between the previous birth weight of the participants and the doses of S/P given is statistically significant.

Majority of the participants who had 5 doses had booking weight of 60-79kg. (P < 0.05). Thus this association between the booking weight of the participants and the doses of S/P given is statistically significant.(mean booking weight 70.2kg)

A higher proportion of participants in both groups were between 1.5m – 1.7m, .i.e. 85.2% and 85.7% respectively. (P < 0.05)Thus this association between the booking height of the participants and the doses of S/P given is statistically significant.(mean booking height 1.59m)

Higher proportion of the participants that took two doses (58.3%) had 1st dose between the 18th-19th weeks of gestation. While most of those that had 5 doses 75.2% had first dose administered to at 16-17 weeks gestation. P > 0.05, hence the alternative hypothesis is rejected. Thus this association between the gestational age when SP was 1st administered to the participants and the doses of S/P given

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is not statistically significant.(mean GA at which S/P was given was 18.02wks)

About half the proportion of the participants that took two doses (60.9%) delivered at > 40 week of gestation. While about half the proportion of those that had 5 doses 50.5% had their delivery at > 40weeks. P < 0.05,. Thus this association between the gestational age when SP was 1st administered to the participants and the doses of S/P given is statistically significant. Still birth was not recorded in any of the groups.(mean GA at delivery was 39.1wks)

Group A and B had 1.4% and 2.2% preterm delivery at 30-34weeks of the original population of 139 respectively. Group A and B had 3.6% and 5.0% preterm delivery at 35-36 weeks of the original population of 139 respectively.

They were excluded from the study without further analysis as preterm delivery was one of the exclusion criteria. Parasitaemia on histological examination was present in a quarter of the total participants in the study i.e. 24.2%. P > 0.05, hence the null hypothesis is accepted. Thus this association between the presence of parasitaemia on histological examination and the doses of S/P given is not statistically significant.

None of the participants had grade 0 and grade 3 parasitaemia. However a higher proportion of those that had parasitaemia had grade 1 parasitaemia. P > 0.05, hence the null hypothesis is accepted. Thus this association between the grades of parasitaemia and the doses of S/P given is not statistically significant (Using active infection, ,prevalence 20% vs 16.2% average prevalence 18.1%). A higher proportion of the participants that took 2 doses (70%) and those that took 5 doses (73.9%) had placenta weight with parasiteamia of 0.4-0.49kg. The P>0.05, hence the null hypothesis is accepted. Thus the association between the placenta weight with parasiteamia and the doses of S/P given is not statistically significant .(Mean wt 0.53 vs 0.51 kg)

A higher proportion of the participants that took two doses (53.3%) and those that took 5 doses (56.5%) had maternal PCV in labour with placenta parasiteamia of 27-30%.P>0.05, hence the null hypothesis is accepted. Thus the association between maternal PCV in labour with placenta parasiteamia and the doses of S/P given is not statistically significant.(Mean PCV 30.6 vs31.7%) Aneamia13.9 vs12.4%

A higher proportion of the participants that took two doses (63.3%) and those that took 5 doses (69.6%) had fetal weight with placenta parasiteamia of 2-2.9kg. P>0.05; while (10%) in group A and (8.7%) of group B with parasiteamia had fetal weight >4kg. Hence the null hypothesis is accepted. Thus the association between fetal weight with placenta parasiteamia and the dose of S/P given is not statistically significant.(Mean fetal weight 2.63 vs2.69kg)

A higher proportion of the participants that took 2 doses (60%) and those that took 5 doses (60.9%) had fetal cord PCV with placenta parasiteamia of 41-45%.P>0.05; hence the null hypothesis is accepted. Thus the association between fetal cord PCV with placenta parasitaemia and the doses of S/P given is not

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statistically significant.(Mean cord PCV 46.8 vs48%)

A higher proportion of the participants that took 2 doses (63.3%) and those that took 5 doses (65.2%) were nulliparous women with placenta parasiraemia. P>0.05; hence the null hypothesis is accepted. Thus the association between parity and the dose of S/P given is statistically not significant. However nulliparity was a risk factor for placenta parasiteamia when compared to other gravidity. Only 36.2 % and 32.8% of the multiparas in group A and B had placenta parasiteamia.

A higher proportion of the participants that took 2 doses (70%) and those that took 5 doses (65.2%) were rural dwellers with placenta parasiteamia. P<0.05; hence the null hypothesis is rejected. Thus, the association between the presence of placenta parasiteamia based on the residential abode and the dose of S/P given is statistically significant. This indicates that the rural dwellers have more placenta parasiteamia compared to urban dwellers (Group A- 30%) and (Group B-34.8%).This findings shows that rural abode is a risk factor for placenta parasiteamia. The coefficient of multivariate determination R2 which shows the proportion of dependent variable in the independent variables (group A and B) is 0.927. Also, the coefficient of multivariate correlation R which shows how dependable the variable is 0.966. These values show that there is no much difference between women who took 2 doses and those who took 5 doses in group A and B respectively. The standard error estimate is 0.0185 (1.85%) variance between variables in group A and B. This value also shows that there are no much difference between participant who took 2 doses and those who took 5 doses in group A and B respectively. The multivariate P-valve which is the significant F is 0.9724. This value is greater than the level of significant 0.05. (P > 0.05), hence the null hypothesis is accepted and there is a no difference between placenta weight with parasiteamia in the two groups (A and B); therefore, the analysis is not statistically significant. This means that there is a relationship between group A and B in the correlation which does not generate any different in the outcome between women who took 2 doses of S/P and those who took 5 doses of S/P.

The coefficient of multivariate determination R2 which shows the proportion of dependent variable in the independent variables (group A and B) is 0.99. Also, the coefficient of multivariate correlation R which shows how dependable the variables are is 0.996. These values show that there is no much difference between women who took 2 doses and those who took 5 doses. The standard error estimate is 0.0167 (1.7%) variance between variables in group A and B. This value also shows that there are no much difference between people who took 2 doses and those who took 5 doses in group A and B respectively. The multivariate P-valve is the significant F which is 0.152. This value is greater than the level of significant 0.05. (P > 0.05), hence the null hypothesis is accepted and there is no difference between maternal in PCV labour with placenta parasiteamia in the two groups

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(A and B); therefore, the analysis is not statistically significant. This means that there is a relationship between group A and B in the correlation which does not generate any different in the outcome between women who took 2 doses of S/P and those who took 5 doses of S/P.

The coefficient of multivariate determination R2 which shows the proportion of dependent variable in the independent variables (group A and B) is 1. Also, the coefficient of multivariate correlation R which shows how dependable the variables are is 1. These values show that there is no difference between women who took 2 doses and those who took 5 doses. The standard error estimate is 0 (0%) variance between variables in group A and B. This value also shows that there is no difference between women who took 2 doses and those who took 5 doses. The multivariate P-valve is the significant F which is 0.078. This valve is greater than the level of significant 0.05. (P > 0.05), hence the null hypothesis is accepted and there is no difference between fetal weight at delivery with placenta parasitaemia in the two groups (A and B); therefore, the analysis is not statistically significant. This means that there is a relationship between group A and B in the correlation which does not generate any different in the outcome between women who took 2 doses of S/P and those who took 5 doses of S/P.

The coefficient of multivariate determination R2 which shows the proportion of dependent variable in the independent variables (group A and B) is 1. Also, the coefficient of multivariate correlation R which shows how dependable the variables are is 1. These values show that there is no difference between women who took 2 doses and those who took 5 doses. The standard error estimate is 0 (0%) variance between variables in group A and B. This value also shows that there is no difference between people who took 2 doses and those who took 5 doses. The multivariate P-valve is the significant F which is 0.078. This value is greater than the level of significant 0.05. (P > 0.05), hence the null hypothesis is accepted and there is no difference between fetal cord PCV with placenta parasiteamia in the two groups (A and B); Therefore, the analysis is not statistically significant. This means that there is a relationship between group A and B in the correlation which does not generate any different in the outcome between women who took 2 doses of S/P and those who took 5 doses of S/P.

The coefficient of multivariate determination R2 which shows the proportion of dependent variable in the independent variables (group A and B) is 1. Also, the coefficient of multivariate correlation R which shows how dependable the variables are is 1. These values show that there is no differences between women who took 2 doses and those who took 5 doses. The standard error estimate is 0 (0%) variance between variables in group A and B. This value also shows that there is no difference between people who took 2 doses and those who took 5 doses. The multivariate P-valve is the significant F which is 0.098. This value is greater than the level of

significant 0.05 (P > 0.05), hence the null hypothesis is accepted and there is no difference between maternal parity with parasitaemia in the two groups (A and B); therefore, the analysis is not statistically significant. This means that there is a relationship between group A and B in the correlation which does not generate any different in the outcome between women who took 2 doses of S/P and those who took 5 doses of S/P. However, 45.3% of the nullipara had placenta parasitaemia which means that the nullipara had more placenta parasitaemia.

The nulliparous women in the two groups have higher percentages (63.3% and 65.2%) in group A and B respectively. This implies nulliparity is a risk factor for placenta parasitaemia. Based on table 6, the mean values and the standard deviations for the maternal PCV in labour with placenta parasitaemia, placenta weight with parasitaemia, fetal cord PCV with placenta parasitaemia and fetal weight with placenta parasitaemia were evaluated.

The percentage mean deviations from both groups for the four parameters considered were further evaluated. The maximum deviation was 3.5% (placenta weight with parasiteamia) and minimum deviation was 2.2% (fetal cord PCV with placenta parasiteamia as shown in table 8.).These percentages are very small and are within an error margin of ±5%

Analyzing the fetal maternal outcome of the study using the four variables above, shows that there is no significant difference between administration of 2 doses (group A) and 5 doses (group B) in the women.

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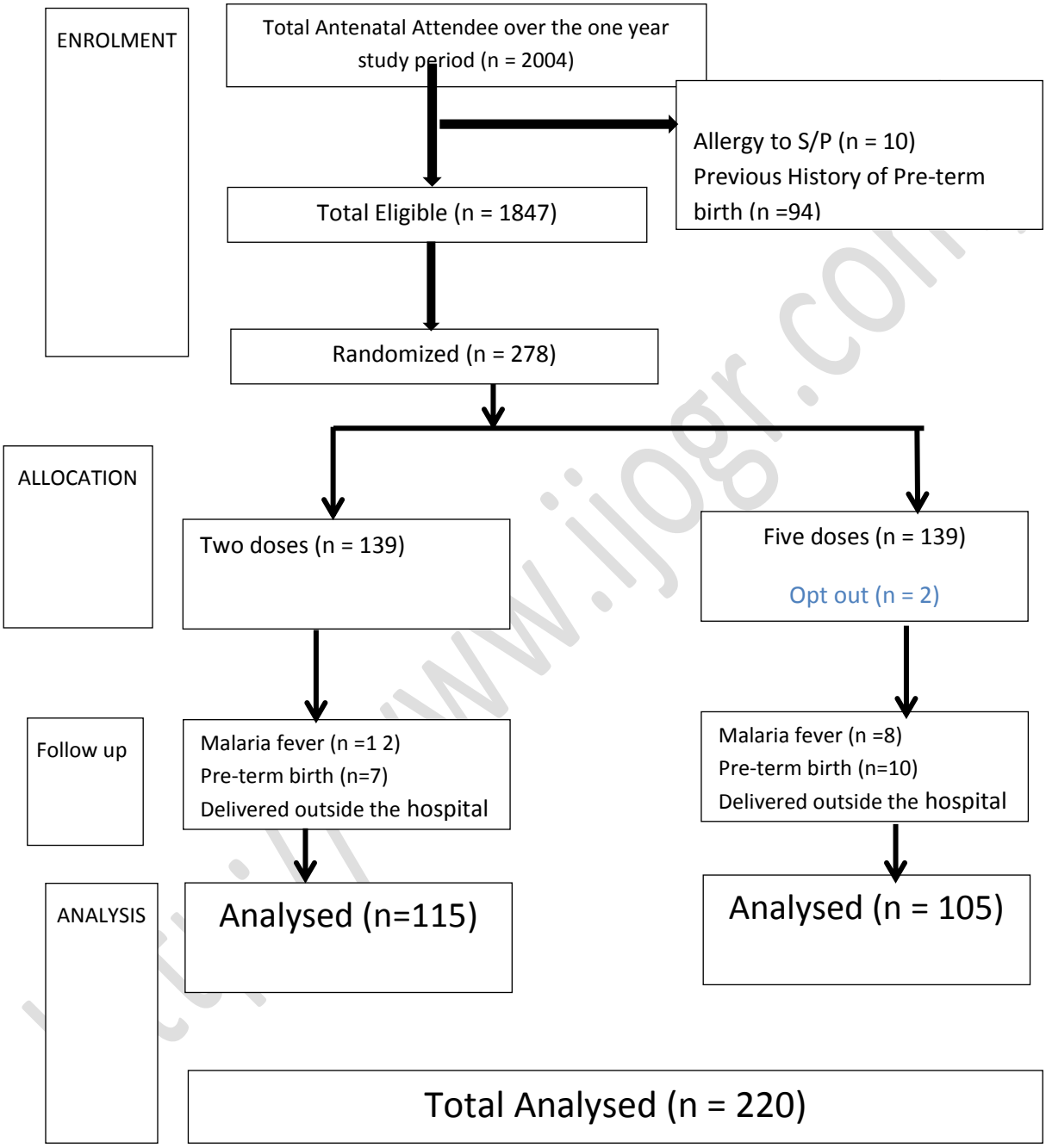

FIGURE 1: *CONSORT FLOW CHART*

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TABLE 1: PROFILE OF THE ENROLLED PARTICIPANTS.

Variables	Group A Frequency n=115	Group B Frequency n=105	X^2 / p-value
Age (Years)	S		
14-19	3 (2.6%)	2 (1.9%)	
20-25	22 (19.1%)	29 (27.6%)	
26-31	50 (43.5%)	42 (40.0%)	
32-37	31 (27.0%)	27 (25.7%)	
>37	9 (7.8%)	5 (4.8%)	2.826/ 0.457
Parity			
Nullipara	27 (23.5%)	20 (19.0%)	
Para 1-4	70 (60.9%)	59 (56.2%)	
≥Para 5	18 (15.6%)	26 (24.8%)	2.987/ 0.323
Marital status			
Married	113 (98.3%)	105 (100.0%)	
Single	2 (1.7%)	0 (0%)	
Separated	0 (0%)	0 (0%)	
Divorced	0 (0%)	0 (0%)	1.843/ 0.225
Participant occupation level	**n= 115**	**n= 105**	
Skill level 0	16 (13.9%)	0 (0.0%)	
Skill level 1	1 (0.9%)	13 (12.4%)	

Skill level 2	38 (33.0%)	50 (47.6%)	
Skill level 3	49 (42.6%)	35 (33.3%)	
Skill level 4	11 (9.6%)	7 (6.7%)	37.838/ 0.061
Educational level of Participants			
No formal education	23 (20%)	27 (25.7%)	
Primary education	48 (41.7%)	31 (29.5%)	
Secondary education	26 (22.6%)	34 (32.4%)	
Tertiary education	18 (15.7%)	13 (12.4%)	5.41/ 0.014
Husband occupation level	**Group A**	**Group B**	**X^2 /p-value**
Skill level 0	5 (4.4%)	4 (3.8%)	
Skill level 1	10 (8.7%)	5 (4.8%)	
Skill level 2	14 (12.2%)	5 (4.8%)	
Skill level 3	35 (30.4%)	44 (41.9%)	
Skill level 4	**51 (44.3%)**	**47 (44.7.%)**	**7.676/ 0.164**
Husband Level of Education			
None	20 (17.4%)	28 (26.7%)	
Primary	53 (46.1%)	35 (33.3%)	
Secondary	33 (28.7%)	36 (34.3%)	
Tertiary	9 (7.8%)	6 (5.7%)	6.608/ 0.088

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Tribe	n= 115	n= 105	
Esan	70(60.9%)	61 (58.1%)	
Bini	11 (9.6%)	5 (4.8%)	
Afemai	19 (16.5%)	26 (24.8%)	
Yoruba	6 (5.2%)	3 (2.9%)	
Igbo	7 (6.1%)	10 (9.4%)	
Hausa	2 (1.7%)	0 (0.0%)	7.047/ 0.347
Religion			
Christian	102 (88.7%)	98 (93.4%)	
Muslims	13 (11.3%)	7 (6.6%)	1.481/ 0.219
Participants Abode			
Urban	39 (33.9%)	22 (21.7%)	
Rural	76 (66.1%)	83 (78.3%)	4.077/0.065

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TABLE 2: Participants awareness of the effect of malaria in pregnancy

Variables	Group A Frequency n=115	Group B Frequency n=105	X^2 / p-value	
Awareness malaria complicates pregnancy				
Yes	80 (69.6%)	89 (84.8%)		
No	35 (30.4%)	16 (15.2%)	6.601/0.064	
Awareness chemoprophylaxis prevent malaria complications				
Yes	88 (76.5%)	63 (60%)		
No	27 (23.5%)	42 (40%)	3.439/0.073	
Use of chemoprophylaxis in previous pregnancy (n = 173)	n = 93	n = 80		
Yes	65 (69.9%)	56 (70%)		
No	28 (30.1%)	24 (30%)	0.000/0.788	

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Table 3: Previous birth weight, booking weight and booking height of participants

	n = 93	n = 80		
Previous birth weight	**Group A**	**Group B**	**X^2 /p-value**	
Can't remember	30 (32.3%)	23 (28.8%)		
<2kg	4 (4.2%)	1 (1.2%)		
2-3kg	13 (14.2%)	18 (22.5%)		
>3kg	46 (49.5%)	38 (47.5%)	2.658/0.0147	
Booking weight	n = 115	n = 105		
40-59kg	13 (11.3%)	7 (6.7%)		
60-79kg	84 (73.0%)	75 (71.4%)		
≥80kg	18 (15.7%)	23 (21.9%)	85.142/0.013	
Booking height	n = 115	n = 105		
<1.5m	9 (7.8%)	6 (5.7%)		
1.5 - 1.7m	98 (85.2%)	90 (85.7%)		
>1.7m	8 (7.0%)	9 (8.6%)	5.179/0.011	

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Table 4: Gestational ages when participants first took S/P and gestational age at delivery

VARIABLE	GROUP A	GROUP B	Total	X^2 /P-value
gestational age when SP was 1st administered	n = 115	n = 105		
16-17	39 (33.9%)	79 (75.2%)	118 (53.6%)	
18-19	67 (58.3%)	15 (14.3%)	82 (37.3%)	
20-21	9 (7.8%)	11 (10.5%)	20 (9.1%)	46.67/0.21
gestational age at delivery 37-40weeks	45(39.1%)	52(49.5%)	97(44.1%)	
>40weeks	70 (60.9%)	53 (50.5%)	123 (55.9%)	1.410/0.006

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Preterm delivery	n = 139	n = 139		
30-34weeks	2 (1.4%)	3 (2.2%)	5 (3.6%)	
35-36weeks	5 (3.6%)	7 (5.0%)	12 (8.6 %)	

Table 5: Presence of parasitaemia on histological examination and the grading in both groups

parasitaemia on histology	**GROUP A**	**GROUP B**	**Total**	**X^2 /P-value**
Present	30 (26.3%)	23 (21.9%)	53 (24.2%)	
Absent	85 (73.7%)	82 (78.1%)	167 (75.8%)	0.439/0.0508
Grades of Parasitaemia				
Grade 0	0 (0%)	0 (0%)	0 (0%)	
Grade 1	23 (76.7%)	17 (73.9%)	40 (75.5%)	
Grade 2	7 (23.3%)	6 (26.1%)	13 (24.5%)	
Grade 3	0 (0%)	0 (0%)	0 (0%)	0.0242/0.623

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Table 6: Association between the use of two and five doses of S/P and placenta weight with parasiteamia, maternal PCV in labour with placenta parasiteamia, fetal weight with placenta parasiteamia, cord PCV with placenta parasiteamia, maternal parity with placenta parasiteamia and residential abode with placenta parasiteamia.

Placenta weight with Parasiteamia (kg)	**GROUP A**	**GROUP B**	**X^2 /p- value**	
	n = 30	n = 23		
≤ 0.39	0	0		
0.4-0.49	21(70%)	17(73.9%)		
0.5-0.59	5 (16.7%)	4 (17.4%)		
0.6-0.69	4 (13.3%)	2 (8.7%)		
.>0.7	0 (0%)	0 (0%)	0.838/0.658	
Maternal PCV in Labour (%)				
27-30	16 (53.3%)	13 (56.5%)		
31-34	7 (23.3%)	5 (21.7%)		
35-38	5 (16.7%)	4 (17.4%)		

>38	2 (6.7%)	1 (4.4%)	0.928/0.821	
Fetal weight at delivery (kg)	n=30	n=23		
2-2.9	19 (63.3%)	16 (69.6%)		
3-4	8 (26.7%)	5 (21.7%)		
>4	3 (10.0%)	2 (8.7%)	1.171/0.557	
Fetal cord PCV (%)				
41-45	18 (60.0%)	14 (60.9%)		
46-50	10 (33.3%)	6 (26.1%)		
56-60	2 (6.7%)	3 (13.0%)	2.639/0.267	
Parity				
Nulliparous	19 (63.3%)	15 (65.2%)		
Para-4	8 (26.7%)	6 (26.1%)		
≥para 5	3 (10.0%)	2 (8.7%)	0.103/0.950	

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Rural	21 (70%)	15 (65.2%)		
Urban	9 (30%)	8 (34.8%)	0.112/0.021	

The association between the above variables did not show statistically significant relationships. They were however further fed into a multivariate model to identify those that had outstanding relationships.

Table 7(a): Multivariate Analysis of Placenta Weight with Parasitaemia

The dependent variable (placenta weight with parasitaemia) is Y while the independent variables to be compared (group A and group B) are x_1 and x_2 respectively as appeared in the table below. Spreadsheet excel solver was used to analyze the multivariate regression analysis.

SUMMARY OUTPUT

Regression Statistics								
Multiple R	0.966131895							
R Square	0.927599807							
Adjusted R Square	0.944800387							
Standard Error	0.0185114513							
Observations	5							
ANOVA								
	Df	*SS*	*MS*	*F*	*Significance F*			
Regression	2	0.001945234	0.000973	0.028383	0.972400193			
Residual	2	0.068534766	0.034267					
Total	4	0.07048						

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	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	0.553945313	0.130383413	4.248587	0.051184	0.007049236	1.11494	0.00705	1.114939861
X Variable 1	0.006679687	0.130383413	0.051231	0.963798	0.554314861	0.567674	0.55431	0.567674236
X Variable 2	0.005078125	0.158635145	0.03201	0.97737	0.687630065	0.677474	0.68763	0.677473815

Table 7 (b): Multivariate Analysis of Maternal PCV in Labour with placenta parasitaemia

SUMMARY OUTPUT

Regression Statistics								
Multiple R	0.995601612							
R Square	0.991222571							
Adjusted R Square	0.973667712							
Standard Error	0.0167423812							
Observations	4							
ANOVA								
	Df	*SS*	*MS*	*F*	*Significance F*			
Regression	2	50.30454545	25.15227	56.46429	0.1523688			
Residual	1	0.445454545	0.445455					
Total	3	50.75						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	42.42727273	1.004164881	42.2513	0.015065	29.66815	55.1863973	29.6681482	55.18639729
X Variable 1	3.772727273	1.129433413	3.34037	0.185178	18.1235	10.5780849	18.123539	10.57808491
X Variable 2	3.672727273	1.328766283	2.764013	0.220997	13.2108	20.5563037	13.210849	20.55630371

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Table 7 (c): Multivariate Analysis of Fetal Weight at Delivery with placenta parasiteamia

SUMMARY OUTPUT

Regression Statistics								
Multiple R	1							
R Square	1							
Adjusted R Square	0.655							
Standard Error	0							
Observations	3							
ANOVA								
	df	*SS*	*MS*	*F*	*Significance F*			
Regression	2	2	1	20.45	0.078			
Residual	0	0	0.655					
Total	2	2						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	4.428571429	0	6.5535	0.07	4.428571	4.428571	4.428571	4.428571429
X Variable 1	0.142857143	0	6.5535	0.065	0.14286	0.14286	0.14286	0.142857143
X Variable 2	0	0	6.5535	0.064	0	0	0	0

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Table 7 (d): Multivariate Analysis of Fetal Cord PCV with placenta parasitaemia

SUMMARY OUTPUT

Regression Statistics								
Multiple R	1							
R Square	1							
Adjusted R Square	0.6134							
Standard Error	0							
Observations	3							
ANOVA								
	Df	*SS*	*MS*	*F*	*Significance F*			
Regression	2	116.6666667	58.33333	15.87	0.078			
Residual	0	0	0.6134					
Total	2	116.6666667						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	60.25	0	6.5535	0.071	60.25	60.25	60.25	60.25
X Variable 1	1.625	0	6.5535	0.087	1.625	1.625	1.625	1.625
X Variable 2	1	0	6.5535	0.09	1	1	1	1

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Table 7 (e): Multivariate Analysis of maternal Parity with placenta parasitaemia

SUMMARY OUTPUT

Regression Statistics								
Multiple R	1							
R Square	1							
Adjusted R Square	0.5367							
Standard Error	0							
Observations	3							
ANOVA								
	df	*SS*	*MS*	*F*	*Significance F*			
Regression	2	14	7	31.6	0.098			
Residual	0	0	0.5367					
Total	2	14						
	Coefficients	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*	*Lower 95.0%*	*Upper 95.0%*
Intercept	2	0	4.5535	0.072	2	2	2	2
X Variable 1	7	0	4.5535	0.057	7	7	7	7
X Variable 2	9	0	4.5535	0.066	9	9	9	9

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Table 8: Comparison of means and standard deviation

		N	Mean	SD	% Mean Deviation
Maternal PCV in labour	Group A	30	7.5	5.8	
	Group B	23	7.23	5.1	3.3
Placenta weight with parasiteamia	Group A	30	0.55	5.9	
	Group B	23	0.57	7.1	3.5
Fetal cord PCV	Group A	30	10	8	
	Group B	23	11.4	7.1	2.2
Fetal weight	**Group A**	**30**	**10**	**8.2**	
	Group B	23	10.09	7.4	2.6

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IV. Discussion

This study compares the prevalence of placenta pararasitaemia and the fetal –maternal out come in two groups of patients taking two doses and five doses of S/P prophylaxis in ISTH.

Malaria has been described as a disease of poverty and under development. It remains a complex and overwhelming health problem, with 300 to 500 million new cases and 2 to 3 million deaths per year. Ninety percent of all deaths attributable to malaria occur in Sub-Saharan Africa. However pregnant women in both endemic and non-endemic areas are highly susceptible. Frequency and severity of complication increase during pregnancy as a result of transient depression of cell mediated immunity.

The prevalence of placenta parasiteamia in group A (2 dose of S/P) was 26.3% and group B (5 doses of S/P) was 21.9 % P =0.0508, there is was no statistically significant association between the use of 2 dose S/P and 5 dose S/P and the presence of placenta parasiteamia in the two groups(P>0.05) as shown in table 5..

The average prevalence of placenta parasiteamia detected on placenta histology in this study is 24.2%. This is comparable with a study done in Mali which shows a prevalence of 24.5% among the participants that had 2 dose of S/P compared to weekly use of chloroquin [77]. In Maiduguri, north eastern Nigeria, Bako and co workers found a prevalence of 33.9%.[82]·Ezebialu recently reported a prevalence of 69.6% after examining 265 placenta in Enugu, south –eastern Nigeria [83]. In the Enugu study two doses of SP was compared with five doses, HIV positive mothers were not excluded from the study. Retroviral disease is associated with immune suppression, infected pregnant women are more likely to develop placenta and peripheral parasiteamia [18]. The non-exclusion of HIV positive pregnant women may have influence the outcome of the study.

In another study done in Ghana in which 3 doses of S/P was compared with 2 doses of S/P prophylaxis the prevalence of placenta parasiteamia was reported to be 11% [78]. This value is low compared to the outcome of this study (24.2%). Irrua is a rural community, 78.1% of the participants in the study reside in rural setting where drainage facilities are poor or are nonexistent and the use of insecticide treated nets less likely.

The wide ranges in reported prevalence of placenta malaria may be due to multiple factors. One factor is the method of diagnosis which could be placenta smear for microscopy, polymerase chain reaction (PCR) and placenta histology which is the gold standard in detecting placenta malaria parasiteamia. Other factors that may explain this variation include intensity of transmission, study population characteristics (age, parity,

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HIV status), use of preventive measures (ITNs), and study design.

Based on placenta parasitaemia, the monthly dosing was not significantly superior to the 2-dose regimen ($P > 0.05$) as in table 5.Similar finding by Hamer and colleagues indicated that the monthly dosing was not more efficacious in reducing placenta parasiteamia than the standard 2-dose regimen in an area where malaria transmission is mesoendemic [85]. Contrarily, Filler and coworkers reported that monthly IPTp-SP was a better option than 2-dose IPTp- SP in areas hyperendemic for malaria [84]. HIV pregnant mothers were not excluded from this study (Filler) which may have weakened the outcome of the conclusion drawn from it.

In group A(2 dose S/P) 76.7% had grade one parasitaemia (active infection) and 23.3% had grade two parasiteamia (active- on- past infections). In group B(5 doses S/P) 73.9% had grade one parasitaemia (active infection) and 26.1% had grade 2 parasitaemia (active on past infection).There was no placentae with grade 0 or grade 3 parasitaemia in the two groups. P =0.623, there is no statistically significant association between the grade of parasiteamia and the use of 2 doses and 5 doses of S/P.

Four variables were used to assess the fetal maternal outcome and the presence of placental parasiteamia (Group A: n=30 and B: n=23) in this study. The variables are placenta weight with parasitaemia, fetal weight with placenta parasitaemia, cord PCV with placenta parasitaemia and maternal PCV in labour with planceta parasitaemia. There was no significant difference in the mean value and the standard deviation values. The maximum deviation was 3.5% (placenta weight with parasitemia) and minimum deviation was 2.2% as in table 8.(maternal PCV in labour with placenta parasitaemia) these percentages are very small and are within an error margin of ±5%.There is no significant difference in the fetal maternal outcome in the two groups (2doses and 5 doses of S/P). In a study done in western Nigeria, Chimere and co reported similar findings, that monthly dosing was not superior to the standard 2 dose regimen in terms of fetal- maternal outcome [86]. A study done in Kenya reported a similar findings [84]. In the Kenya study HIV positive women were not excluded.

Preterm delivery was an exclusion criteria in this study. 17 pregnant women had preterm birth 5.0% in original group A (n=139) and 7.2% in group B (n=139). They were not analyzed further but the cause of preterm delivery cannot be tied to the use of S/P which has been shown to be safe in pregnancy.

Using a multivariate analysis (table 6a-e) to analyze the association between the placentae with parasitaemia and the fetal weight,placental weight,fetal cord PCV and maternal PCV in labour; it shows that there is a good correlation among the variables (R and $R^2 \approx 1$). Also, the p-values in all the variables are greater than the level of significant (P >0.05). The null hypothesis is therefore accepted indicating that there is no difference between the administration of 2 doses and 5 doses of S/P; hence, the analysis is statistically insignificant.

The main effect of placental parasitaemia on the babies is the reduction in the birth weight. This is consistent with the observations from other malaria endemic countries [6,34,69], but not shown in this study. Placenta parasitaemia in the mothers was found to be significantly associated with lower maternal heamatocrit., this also was not showed in this study. However, this is not unexpected as the association of malaria in pregnancy and low hematocrit has been recognized and reported by previous workers [87]. The drop in haematocrit occurs as a result of the fact that parasitized and unparasitized erythrocytes are destroyed by the spleen during malaria infection.

Identification of risk factor for placental malaria is essential as it helps program managers in implementing policies that effectively utilize the scarce resources to reduce the burden of the disease .Placenta is an organ that develops during pregnancy, primagravida who has acquired immunity against malaria would not have developed immunity against the CS-A binding parasite population. It therefore suggests that parity is an important predictor of placental malaria. This further emphasizes the need for the use of insecticide-treated nets.

The finding of significant association between rural residents and placental malaria is an important one that may affect program designers and implementation. Most of the developmental program for malaria eradication is concentrated in urban cities so that rural dwellers are likely to live in dirty environment and more prone to malaria.

The major strength of this study was the utilization of histological analysis which has been shown to have a superior detection rate compared to other means of diagnosing malaria. Another strength of this study was that S/P was taken under direct observation therapy. The interpretation of the study findings should however consider some limitations. This study was done in a tertiary centre that is more likely to be accessed by women of high socio-economic class. The rural poor dwellers who are likely to be affected by malaria are more likely to attend maternity homes, faith healing centers, Traditional Birth Attendance (TBA), and small clinics either due to ignorance or financial reasons.

However, the findings of the present study are relevant as it has thrown light unto the burden of the condition and has also shown that two doses of S/P is as effective as five doses hence reducing the cost of antenatal care.

The observed impact of malaria on the mothers and their new born add justification for promoting use of malaria preventive measures in pregnancy. The tools for achieving effective malaria control are now available. These include use of ITNs, IPTp and effective treatment. It is essential that all stake holders combine efforts to ensure successful implementation in the deployment of those various tools in order to achieve a reduction in the burden of malaria in pregnancy in Nigeria.

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V. CONCLUSION

Sulphadoxine-pyrimethamine is effective in protecting pregnant women against malaria. The result from the study shows that two doses of intermittent preventive therapy of S/P is as effective as five doses in reducing placenta parasiteamia with improved fetal-maternal outcome. Maternal parity and participant residential abode were the most predisposing factor to placental malaria. The prevalence of placental parasiteamia on the average was found to be 24.2%. This finding underscores the need for a focused and concerted effort to address the control of malaria during pregnancy. This study indicates that two- dose therapy is as efficacious as five- dose therapy. Direct observational therapy with two doses may be less challenging than with five doses. Compliance and cost effectiveness are also better with two compared to five doses.

RECOMMENDATION

Health education program for pregnant women in these areas should be intensified especially in women of low educational status on the need to use insecticide treated net and to seek antenatal care in health facility when pregnant instead of going to TBA, maternity homes and faith healing centres. Direct observational therapy should be employed when administering S/P in which pregnant women would be made to take the drug under direct observation by the nurses in the antenatal clinic. This would help in improving the compliance rate since some women may get the drug and not use it.

Health workers should be provided continuing education and training to improve their knowledge of IPTp-S/P strategy and directly observed therapy (DOT) scheme. Sulphadoxine-pyrimethamine should be made available in various antenatal clinics free or at a subsidized rate.

Malaria in pregnancy has devastating effects on the mother and fetus. Prevention remains the key to limiting morbidity and mortality. S/P has been shown to be effective as chemoprophylaxis in pregnancy. Compliance, efficacy and optimum dose have remained unresolved.

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APPENDIX A:

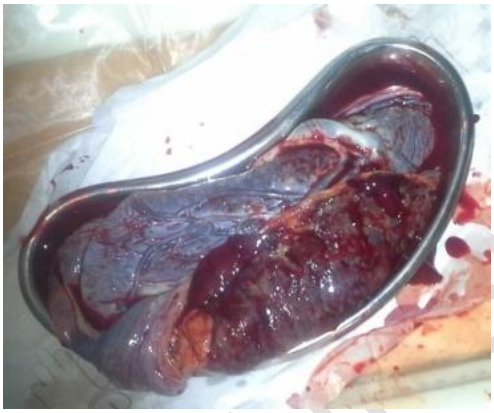
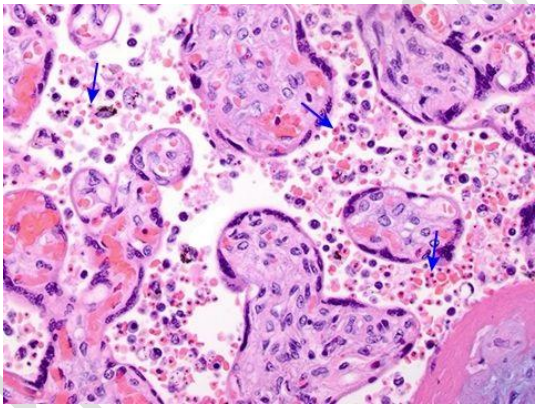


Fig. 2. placenta



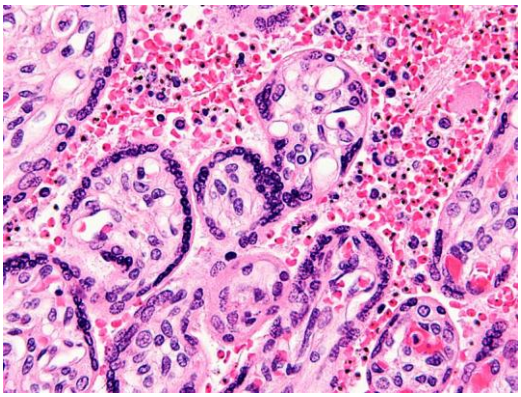


Fig. 3 and 34. Micrograph showing malaria parasite within the intervillous space.