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Anaemia in Pregnancy and Malaria Parasitaemia in Women at Delivery after 2 Doses of Sulfadoxine-Pyrimethamine Combination in Jos.

Ozele, Kingsley Chukwuka (MBBS, FMCOG); Ozele Nonyelim (BSC, FMLSCN)

Consultant Special Grade 1 (Obstetrics and Gynaecology) and Head Medicine and Health Services Department, National Institute for Policy and Strategic Studies Kuru Jos Plateau State, (NVRI) Vom.[1]
Chief Medical Laboratory Scientist Biochemistry Division National Vertinary Research Institute (NVRI) Vom.[2]

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Corresponding Author
Dr Ozele KC MBBS FMCOG
E-mail: *kingsleyozele9@gmail.com*

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ABSTRACT

Background: Malaria infection in pregnancy especially by Plasmodium falciparium leads to parasite sequestration in the maternal placental vascular space with consequent maternal anaemia and delivery of infant with low birth weight.
Objective: The objective of the study is to determine if significant differences exist in the occurrence of anaemia, malaria parasitaemia, placenta parasitisation and low birth weight in women at delivery after administering 2 doses of sulfadoxine-pyrimethamine combination at JUTH when compared to those women that had none or one dose of sulfadoxine-pyrimethamine.
Design: Hospital based descriptive cross sectional study.
Methodology: Consenting 171 parturients in control Group who booked for ANC at JUTH were recruited during the last four weeks of pregnancy at the antenatal clinic and a pre – structured questionnaire administered. Consenting 167 parturients in the study Group were recruited as they present in labour ward. Blood samples were collected as the women present in labour at the labour suite. Placental blood was collected after delivery of the placenta
Result: Statistically significant higher prevalence of maternal malaria parasitaemia in the none or once SP study group compared to twice SP control group. x^2= 32.937, L.R= 33.660, P Value=0.000
The prevalence of anaemia before delivery was higher in the none or once SP study group compared to twice SP control group. But this was not statistically significant. X^2=0.823, L.R= 0.826, P Value=0.364(Fisher exact test)
Statistically significant higher prevalence of placental parasitisation in the none or once SP study group compared to twice SP control group. X^2=31.335, L.R= 34.725, P Value=0.000
Statistically significant higher prevalence of low birth weight (LBW) in the none or once SP study group compared to twice SP control group. X^2=5.197, L.R= 7.120, P Value=0.029 (Fisher exact test)
Conclusion: 2 doses of SP is more effective than none or once SP in preventing malaria parasitaemia, placental parasitisation and reducing the prevalence of low birth weight in pregnancy.

INTRODUCTION

1.1 Malaria Burden and Prevention in Pregnancy.

The female Anopheles species of the mosquito is the vector that is responsible for the transmission of the plasmodium parasite from human to human through its bite. There are four main types of parasites that cause malaria but Plasmodium falciparium is the most common and causes the most severe infection[1].

According to statistics by the World Health Organization (WHO), malaria is the largest parasitic disease killer globally, killing 2 persons every minute[1]. Globally, malaria causes 1-3 million deaths per year and 90% of such deaths occur in sub-Saharan Africa. Children and women are the most affected.[1] In the past, several chemoprophylaxis like chloroquine, proquanil, pyrimethamine and mefloquine had been used in pregnancy but problems of rising levels of plasmodium falciparium resistance to most of these drugs has become an issue.

The WHO, in a policy for prevention and control of malaria recommends that the prevention of malaria during pregnancy in areas of stable transmission should emphasize a preventive package of Intermittent Preventive Therapy (IPT), insecticide treated bed nets (ITN_s) and ensure effective case management of malaria illness and anaemia[1]. Intermittent Preventive Therapy is a public health intervention aimed at preventing malaria episodes in Infants (IPT_I), Children (IPT_C), School Children (IPT_{SC}) and pregnant women (IPT_P). The intervention builds on two tested malaria control strategies that is to clear existing parasites and prevents new infections. Intermittent preventive therapy in pregnant women involves the administration of a single curative dose of an efficacious antimalarial drug at predefined intervals (at least twice during pregnancy) regardless of whether or not the woman is manifesting with symptoms of malaria, with the intent to protect a pregnant woman against malaria. The drug is administered under supervision during antenatal care (ANC) visit. Sulfadoxine –pyrimethamine is the combination currently recommended by the WHO because of its safety and efficacy. [2, 3] It involves the use of sulfadoxine -pyrimethamine antimalarials at treatment doses given at predefined intervals to clear a presumed burden of parasites.

IPT of malaria during pregnancy is based on the assumption that every pregnant woman living in areas of high malaria transmission has malaria parasites in her blood or placenta, whether or not she has symptoms of malaria and could affect her baby.[4]

Malaria infection contributes to as much as 15% of maternal anaemia, 14% of low birth weight infants, 30% of preventable low birth weight, 70% of intrauterine growth restriction, 30% of premature delivery and 8% of infant mortality.[5, 6] The administration of SP twice in pregnancy has been proven to reduce maternal anaemia by 39%, placental malaria by 56% and low birth weight by 43%[7]

Two doses of SP are required to achieve optimal benefit in most women. A third dose causes no additional risk and is advocated for patients with lower natural acquired immunity to malaria like those with HIV and sickle cell disease in pregnancy.[7,8, 9]

Nigeria has adopted the use of IPT with SP since 2005[6]. Malaria infection during pregnancy contributes significantly to anaemia in pregnancy and low birth weight. Antenatal anaemia has shown positive correlation with low birth weight and high infant mortality rate[8,9]. The use of effective antimalarial drugs during pregnancy has been found to lower the frequency of low birth weight and infant mortality rate.[9, 10] The use of IPT is a promising approach in malaria control because it has shown potential to provide some of the benefits of sustained prophylaxis for women.[11]

1.2 Statement of the Problem

Malaria infestation in pregnancy especially by Plasmodium falciparium leads to parasite sequestration in the maternal placental vascular space, with consequent maternal anaemia and infant low birth weight (LBW) due to both prematurity and intrauterine growth restriction (IUGR). [5, 6, 12] LBW is known to be the most important risk factor for infant mortality.[13] The WHO has recommended the use of intermittent preventive therapy with at least 2 doses of SP and other additional prevention measures during pregnancy. But some pregnant women register for antenatal care at gestational ages when it is impossible for them to have 2 doses of SP before 36 weeks of gestation. It also pertinent to note that while some have their antenatal care where SP is not given routinely, some others react to sulphur-based drugs and hence may not have had the routine 2 doses of SP during pregnancy. The effect of this observation in relation to the occurrence of anaemia in pregnancy as well as malaria parasitaemia in women at delivery in JUTH create an established medical question, for which this study provides an answer.

1.3 Justification of the Study

In areas of endemic transmission, malaria in pregnancy is associated with severe maternal anaemia and low birth weight babies. The WHO has recommended the use of intermittent preventive therapy with at least 2 doses of SP and other additional preventive measures during pregnancy.[3] Studies in Kenya, Malawi and Mozambique have shown that IPT with at 2 curative doses of SP is highly effective in reducing maternal anaemia and placental malaria infection at delivery and also the number of low birth weight babies.[14] Some pregnant women do not get the recommended 2 doses of SP because of late booking for ANC. Some also book at centres that have not yet adopted this WHO

recommendation and as a result are not given 2 doses of SP. Others react to sulphur-based drugs and hence may not have had the routine 2 doses of SP during pregnancy. But some of these women come in and deliver in our facility. This study is aimed at assessing if the risk of anaemia and malaria parasitaemia on this group of mothers and risk of low birth weights and placental malaria parasitaemia for their babies are significantly higher than in those parturients who had 2 doses of SP.

Prevention of malaria during pregnancy is one of the major interventions to reduce maternal and infant morbidity and mortality with the aim of contributing to achieving the fourth (two-thirds reduction in child mortality rate), fifth (three-fourth reduction in maternal mortality rate) and sixth (Combat HIV/AIDS, malaria and other diseases) millennium development goals (MDG's).[3]

The findings from this study will be useful in assessing the effectiveness of the intermittent preventive therapy and aid further actions. The study will help in health planning. It is for this reason that this dissertation: **Anaemia in pregnancy and malaria parasitaemia in women at delivery after 2 doses of sulfadoxine-pyrimethamine combination at JUTH** is being conducted.

1.4 AIM

GENERAL: The aim of the study is to determine if significant differences exist in the occurrence of anaemia, malaria parasitaemia, birth weights and placental parasitaemia in women at delivery after 2 doses of sulfadoxine-pyrimethamine combination at JUTH when compared to those women that had none or one dose of sulfadoxine-pyrimethamine combination.

Objectives:

This study serves the objective of identifying the prevalence of malaria parasitaemia and specie types involved in the study group

Also, it identifies the prevalence of anaemia before delivery at JUTH in the study group

In addition to the forgoing, it further identifies the prevalence of low birth weight and that of placental parasitisation in the study group.

Finally, it measures the above four indices in control group and find out whether there are statistically significant difference in the two groups.

1.5 Working Hypothesis

The prevalence of malaria parasitaemia, placental parasitisation, anaemia and LBW are higher in parturients who did not receive the recommended doses of SP compared to those that received 2 doses of SP.

2. LITERATURE REVIEW

2.1 Prevalence

Each year, there are approximately 350–500 million cases of malaria,[1] killing between one and three million people, the majority of whom are young children in sub-Saharan Africa.[2] Ninety percent of malaria-related deaths occur in sub-Saharan Africa[2]. Malaria in pregnancy is also a major public health problem in endemic tropical and subtropical countries and a major cause of foetal and maternal morbidity.[15] Anaemia in pregnancy is an important public health problem worldwide. It is the most prominent haematological manifestation of malaria infection. This results from destruction of red blood cells (both parasitized and unparasitized), reduced feeding during malaria episodes, suppression of haemopoiesis, intense sequestration of infected erythrocytes in the placenta and other contributory factors.[8] It is worse with Plasmodium falciparium which invades erythrocytes of all ages.[16] Other causes of anaemia are poor nutrition, deficiencies of iron and other micro nutrients, hookworm infestation, and schistosomiasis disease including HIV infection and haemoglobinopathies are additional factors.[17] WHO estimates that more than half of pregnant women in the World have a haemoglobin level indicative of anaemia (< 11.0gldl), the prevalence may however be as high as 56 or 61% in developing countries.[18]

A prevalence of 59.9% of malaria parasitaemia and anaemia of 62.4% was found in a cross sectional study involving 272 pregnant women in a community study in Ebonyi State.[19] However these patients were not followed up until delivery so as to assess the impact of asymptomatic maternal malaria parasitaemia on foeto-maternal outcome. Nonetheless, this prevalence rate is comparable to others in Libreville Gabon (57%),[20] and in Enugu Nigeria (58.4%).[21]

In a study at Obafemi Awolowo University Teaching Hospital Ile Ife, malaria parasitaemia of 21.1% was noted. Thirty-six (36%) of the women had anaemia.[22] Those with positive smear were treated with 600mg of chloroquine and after re-testing 2 weeks later, were found to be malaria parasite negative.[22] This study followed up the patients after an intervention but the sample size was small and now widespread resistance to chloroquine is reported.

Also in a comparative experimental study in south western Nigeria involving 294 participants, who were randomised into sulfadoxine-pyrimethamine SP and pyrimethamine group, the result showed that at 34 weeks of gestation 35.3% and 6.6% of malaria parasitaemia were found in the pyrimethamine and SP group respectively, which was statistically significant.[23] There were also more participants with haemoglobin concentration less than 8g/dl at 34 weeks in the pyrimethamine group compared to the SP group. Participants were given pyrimethamine and sulfadoxine-pyrimethamine in the 2nd and early 3rd trimesters[23]. Findings from this study in the southwest have shown

that 2 doses of SP for the prevention of malaria in pregnancy is associated with a significant lower incidence of malaria parasitaemia, maternal anaemia in pregnancy compared to weekly 25mg of pyrimethamine.[23] But birth weights and placental malaria parasitaemia were not assessed and compared at delivery.

In a multicentre study conducted for peripartum malaria in Nigeria, 21.6% of prevalence of malaria parasitaemia (maternal and /or placental) was found.[24] Reduction in maternal haematocrit and higher proportion of LBW babies were also found in those with malaria parasitaemia.

A cross sectional study in Maiduguri North Eastern Nigeria using 437 women at delivery found a prevalence of 33.9% placental malaria, while cord parasitaemia and maternal parasitaemia were 16.2% and 30.7% respectively.[25]

Jos University Teaching Hospital (JUTH), is located in Jos, the Plateau State capital. Jos Plateau lies between latitude 7^0 and 11^0 North and Longitude 70^0 and 250^0 east. This region is on a height of 1,200m above sea level.[26] IPT has been adopted in JUTH. There is however no local study from this area.

2.2 Pathophysiology

A mosquito infests a person by taking a blood meal. First, sporozoites enter the bloodstream, and migrate to the liver. They infect liver cells (hepatocytes), where they multiply into merozoites, rupture the liver cells, and escape back into the bloodstream. Then, the merozoites infect red blood cells, where they develop into ring forms, then trophozoites (a feeding stage), then schizonts (a reproduction stage), and then back into merozoites. Sexual forms called gametocytes are also produced which, if taken up by a mosquito, will infect the insect and continue the life cycle [27, 31].

Malaria in humans develops via two phases: an exoerythrocytic and an erythrocytic phase[31]. The exoerythrocytic phase involves infection of the hepatic system, whereas the erythrocytic phase involves infection of the erythrocytes, or red blood cells. 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. Within 30 minutes of being introduced into the human host, the sporozoites infect hepatocytes, multiplying asexually and asymptomatically for a period of 6–15 days. Once 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, thus beginning the erythrocytic stage of the life cycle.[27] The parasite escapes from the liver undetected by wrapping itself in the cell membrane of the infected host liver cell.[28]

Within the red blood cells, the parasites multiply further, again asexually, periodically breaking out of their hosts 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.

Some *P. vivax* and *P. ovale* sporozoites do not immediately develop into exoerythrocytic-phase merozoites, but instead produce hypnozoites that remain dormant for periods ranging from several months (6–12 months is typical) to as long as three years. After a period of dormancy, they reactivate and produce merozoites. Hypnozoites are responsible for long incubation and late relapses in these two species of malaria.[29]

The parasite is relatively protected from attack by the body's immune system because for most of its human life cycle it resides within the liver and blood cells and is relatively invisible to immune surveillance. However, circulating infected blood cells are destroyed in the spleen. To avoid this fate, the *P. falciparum* parasite displays adhesive proteins on the surface of the infected blood cells, causing the blood cells to stick to the walls of small blood vessels, thereby sequestering the parasite from passage through the general circulation and the spleen.[30] This *stickiness* is the main factor giving rise to hemorrhagic complications of malaria. High endothelial venules can be blocked by the attachment of masses of these infected red blood cells. The blockage of these vessels causes symptoms such as in placental and cerebral malaria. In cerebral malaria the sequestrated red blood cells can breach the blood brain barrier possibly leading to coma.[31]

Although the red blood cell surface adhesive proteins (called PfEMP1, for *Plasmodium falciparium* erythrocyte membrane protein 1) are exposed to the immune system, they do not serve as good immune targets because of their extreme diversity; there are at least 60 variations of the protein within a single parasite and effectively limitless versions within parasite populations.[31,32] The parasite switches between a broad repertoire of PfEMP1 surface proteins, thus staying one step ahead of the pursuing immune system.

Some merozoites turn into male and female gametocytes. If a mosquito pierces the skin of an infected person, it potentially picks up gametocytes within the blood. Fertilization and sexual recombination of the parasite occurs in the mosquito's gut, thereby defining the mosquito as the definitive host of the disease. New sporozoites develop and travel to the mosquito's salivary gland, completing the cycle. Pregnant women are especially attractive to the mosquitoes,[32] and malaria in pregnant women is an important cause of stillbirths, infant mortality and low birth weight,[33] particularly in *P. falciparum* infection, but also in other species infection, such as *P. vivax*.[33]

2.3 Placental Malaria

Currently, susceptibility to *Plasmodium* parasitaemia has been linked to the level of antibodies to placental sequestrated parasites.[34] Indeed these parasites preferentially adhere to chondroitin sulphate-A receptors

(CSA) expressed by the syncytiotrophoblasts in the placenta.[35] Women in their first and second pregnancies are more susceptible as anti adhesion antibodies against CSA binding parasites develop after successive pregnancies.[36] The presence of parasites in peripheral blood without symptoms is common in hyper-endemic areas, and is associated with chronic anaemia and placental sequestration .[37]

2.4 Malaria and Anaemia in Pregnant Women

Malaria infection caused by *Plasmodium falciparum* is a major cause of fever and anaemia in pregnant women resident in hyper endemic areas of Africa. Basically, this is as a result of reduced immunity to malaria in pregnancy[38], making the pregnant women prone to severe malaria attack and subsequently anaemia. It has been shown that severe anaemia was more than twice as common in women with peripheral parasitaemia as in those without parasitaemia.[39] Incidentally malaria infection is more rampant among the primigravidae and secundigravidae than the multigravidae.[21] The preferential susceptibility of these sets of pregnant women may be related to some evidence that immunosuppression associated with pregnancy, occurs more in the first than subsequent pregnancies.[40, 41, 42.] Previously, the depression of cell mediated immune response to *Plasmodium falciparum* antigens has been implicated in this phenomenon.[41] Age has also been implicated as epidemiological studies have shown that malaria in pregnancy is more prevalent in younger than older age groups,[10,37,43,44]. Malaria infection during pregnancy contributes significantly to anaemia in pregnancy and low birth weight babies.[45] Antenatal anaemia has shown positive correlation with low birth weight (LBW) and high infant mortality rate (IMR). [11, 28]

2.5 Consequences of Malaria in Pregnancy

In Africa, malaria is highly endemic and is the leading cause of morbidity and mortality. It contributes 4—19% to low birth weight, 3—15% to maternal anaemia, and 3—8% to infant deaths, while maternal anaemia contributes 7—18% to low birth weight.[27-29]

2.6 Diagnosis

2.6.1 Microscopy

Staining thick and thin blood films on a glass slide to visualize the malaria parasite microscopically is the method of diagnosis of malaria. The patient's finger is cleaned with alcohol, allowed to dry and then the side of the fingertip is pricked with a sharp sterile lancet or needle and two drops of blood are placed on a glass slide. To prepare a thick blood film, a blood spot is stirred in a circular motion with the corner of the slide, taking care not make the preparation too thick, and allowed to dry without fixative. As they are unfixed the red cells lyse when a water based stain is applied. A thin blood film is prepared by immediately placing the smooth edge of a spreader slide in the drop of blood, adjusting the angle between slide and spreader to 45°, and then smearing the blood with a swift and steady sweep along the surface. The film is then allowed to air dry and is fixed with methanol. Blood smears are stained using Giemsa stain and parasites are counted against 100 leukocytes and expressed as number of parasites/ml of blood assuming a standard leukocyte count of 8000/ml of blood. A blood smear is negative when minimum of 100 high power fields is examined with no parasites seen. It is positive when parasites are seen

Parasite density is calculated as mean geometric mean parasite density (GMPD/ml). Larger volume of blood is examined in the thick film, so it is more sensitive than the thin film (down to around 40 parasites per µL or 1 parasite per 200 white blood cells) although examination of the thick film requires more expertise to read[46].

The simple, direct microscopic observation of blood specimens to observe the malaria parasite is still the gold standard for malaria diagnosis[47].

2.6.2 Molecular methods

The polymerase chain reaction (PCR) allows the specific amplification of a selected region of the malarial genome.[48] This technique is highly specific and sensitive (1-5 parasite/mL of blood) and permits genotyping.[49, 50] Furthermore, PCR using single nucleotide polymorphism (SNP) analysis allows the detection of drug resistant parasites and mixed infections. [51, 52, 53] However, PCR is expensive and requires a sophisticated laboratory manned with well-trained staff. This is not available in our facility

2.6.3 Rapid methods

Detection in patient samples of malaria parasite antigens such as histidine rich protein II (HRP-II) or plasmodium lactate dehydrogenase (pLDH) can be performed by rapid, point-of-care tests based on immunochromatographic methods. There are many commercially-available rapid tests including Para Sight F[54,55] and Paracheck, Binax NOW P.f./ P.v. and OptiMAL (Flow Inc., USA).[56,57,58]

The advantages of these tests are that they are quick to perform and have high sensitivity.[57, 59] The disadvantages of the rapid format are the relatively high cost, the inability of some tests to distinguish malaria species, and manufacturing variation.[58] Those based on HRP II detection may give positive results in the convalescent phase of the illness due to the persistence of HRP II in the blood after parasite clearance.[60]

2.6.4 Quantitative Buffy Coat method

Quantitative buffy coat (QBC; Becton Dickinson, USA) is a method for identifying the malarial parasite in the peripheral blood. It involves staining of the centrifuged

and compressed red cell layer with acridine orange and its examination under an ultraviolet (UV) light source[60]. Blood is collected (from a finger prick) in a haematocrit tube containing acridine orange and anticoagulant. The haematocrit tube is centrifuged at 12,000 g for 5 min and immediately examined using a microscope equipped with a UV light source.

The parasite nucleic acid fluorescence bright green and the cytoplasm appears yellow-orange[60]. This test has sensitivity similar to the conventional thick blood film microscopic methods. It is reliable and user-friendly and should be used together with thick blood film microscopic screening. However, QBC requires specialized instrumentation, has a higher cost than microscopic methods and is poor at species determination and parasite quantification[60].

2.6.5 Serological methods

Serological tests for the diagnosis of malaria infection rely on the detection of antibodies against asexual blood stages of the malaria parasite. The first serological test used for the detection of malaria antibodies was the immunofluorescence assay, often abbreviated to IFA.[61] This method uses specific antigen or crude antigen prepared on a slide, coated and kept at -30^0C until use, and quantifies both IgG and IgM antibodies in patient serum samples. Titres >1:20 are classified as positive, and those below 1:20 classified as of doubtful significance. High titres (>1:200) represent strong evidence of a recent infection. Serological tests provide retrospective confirmation of malaria infection or a history of infection, and are useful in epidemiology surveys and the screening of blood collected for blood banks. Nevertheless, the utility of serological methods for the diagnosis of acute malaria infection is limited owing to the delay in antibodies development, lack of species confirmation and the need for fluorescence (UV) microscope.[62]

2.6.6 Diagnosis Of Placental Malaria Parasitaemia

There are two main methods of diagnosing placental malaria parasitisation. These are microscopy or histology.

2.6.6A Microscopy: Placental blood is collected within an hour after child-birth by incising the cleaned maternal surface (basal plate) of the placenta, and drawing 5ml of blood welling from the incision using a sterile syringe and needle. The placental blood is then processed as described above.

2.6.6B Histology: Immediately following delivery, the placenta is obtained and a large biopsy specimen of placental tissue (2 by 2 by 1 cm) is fixed in 10% neutral buffered formalin for histopathological studies. Fixed placental biopsies are transferred to the histopathology laboratory where they were processed, embedded in paraffin wax and sectioned onto slides by standard techniques. Sections will later be stained with haematoxylin- eosin stain for detection of active and past infections. One thousand intervillous cells (IVS) are counted to determine the level of parasitaemia in placenta tissue sections. Past infection is defined as the presence of malaria pigment in fibrin or monocyte /macrophage without malaria parasites [63]. Active infection is when malaria parasite is seen with or without pigments. It is negative when neither is seen. Sections may also be observed under polarised light to assess the presence of malaria pigment[64]

Placental histology is considered the *gold standard* of malaria diagnosis in pregnancy for epidemiological or biological study purposes, because it can show signs of active, active chronic or past infections.[65, 66] However, it is expensive and it is not done routinely at the Jos University Teaching Hospital.

2.7 Prevention

Methods used to prevent the spread of disease, or to protect individuals in areas where malaria is endemic include prophylactic drugs, mosquito eradication, and the prevention of mosquito bites[10].

In the past decade, strategies have been developed to more effectively control the adverse effects of malaria during pregnancy. The African Summit on Roll Back Malaria (RBM) in April 2000 adopted the Abuja Declaration in which regional leaders committed to ensuring that sixty percent of pregnant women in malaria-endemic communities accessed effective prevention and treatment of malaria by 2005. The following approaches were to be used:

1. Supporting and promoting access to correct, affordable and appropriate treatment within twenty-four hours of the onset of symptoms.
2. Supporting and promoting access to a suitable combination of personal and community protective measures such as Insecticide Treated Nets (ITNs).
3. Supporting and promoting the use of malaria preventive measures such as chemoprophylaxis or intermittent preventive treatment for pregnant women (IPTp).

The WHO recommended that the policy for the prevention of malaria during pregnancy in areas of stable transmission should emphasize a preventive package of Intermittent Preventive Treatment (IPT) and Insecticide Treated bed Nets (ITN's) and ensure effective case management of malaria illness and anaemia. IPT is the use of anti-malarial drugs given in treatment doses at predefined intervals to clear a presumed burden of parasites. IPT of malaria during pregnancy (IPTp) is based on the assumption that every pregnant woman living in areas of high malaria transmission has malaria parasites in her blood or placenta, whether or not she has symptoms of malaria.

The IPT package means that all pregnant women in areas of stable malaria transmission should receive at least two doses of IPT after quickening, that is, after 16 weeks gestation.

The most effective drug for IPT currently is Sulphadoxine Pyrimethamine (SP) because of its safety for use during pregnancy, effectiveness in reproductive-age women, and the feasibility for use in programs as it can be delivered as a single- dose treatment under direct observation (DOT) by the health worker.

3. SUBJECTS, MATERIALS AND METHOD

3.1 Study Area.

This is a hospital-based study conducted at the Maternity Unit of the Department of Obstetrics and Gynaecology, Jos University Teaching Hospital (JUTH).

JUTH is a tertiary health institution located at its permanent site at Lamingo Jos, the Plateau State capital. It is one of the three teaching hospitals in the North-central zone of Nigeria, although there are Federal Medical Centres (FMCs) in the remaining states within the geo-political zone.

Plateau State lies between latitude 7^0 and 11^0 North and Longitude 70^0 and 250^0 east. The capital city is a pear shape upland known as Jos Plateau. This upland stretches for approximately 104km from north to south, and 80km from east to west, covering an area of about 8,600sqkm[26].

This region has a height of 1,200m above sea level.[26] Plateau State has over 30 different ethnic groups.[26] The 1991 Nigerian census puts the population of Plateau State at 2,959,588 with 1,031,662 being females.[26]

The Departmental protocol for malaria chemoprophylaxis is the intermittent preventive treatment using sulfadoxine-pyrimethamine combination. 2 doses are given. The first is after quickening and the second at least 4weeks after the second but before the last 4 weeks of pregnancy. A third dose is usually given to some patients like those with HIV, and sickle cell disease in pregnancy that is if the HIV positive pregnant woman is not on cotrimoxazole[7].

3.2 Study Population

The study population are women presenting in labour at the Jos University Teaching Hospital, North Central Nigeria.

3.3 Study Design

The study is a prospective, descriptive cross sectional hospital based study conducted over a six-month period (June- December, 2011)

Study Group: Delivery at 37-42 weeks in

1. Women who received 1 dose of SP because of late booking
2. Women who did not receive any dose of SP because they were unbooked
3. Women who did not receive any dose of SP because they booked very late in pregnancy
4. Women who did not receive any dose of SP because they booked for antenatal care elsewhere where they were not given SP.

Control Group: Shall include women delivering at 37-42weeks who received 2 doses of SP in the index pregnancy.

Consenting parturients in Control Group who booked for ANC with JUTH were recruited during the last four weeks of pregnancy at the antenatal clinic and a pre–structured questionnaire administered. Consenting parturients in the Study group were recruited as they present in labour ward. Blood sample was collected as the women present in labour at the labour suite. Placental blood was collected within 1 minute of delivery of the placenta

3.3.2 Exclusion Criteria

The following categories of parturients were excluded from the study:

1. Sickle cell Disease patients
2. Multiple pregnancies
3. Women with severe preeclampsia
4. Women with Intrauterine foetal death
5. Women with chronic anaemia from other causes like poor nutrition, if readily ascertained from history and or physical examination
6. Women who are none compliant on haematinics
7. Preterm and post term deliveries
8. Women who decline to participate in the study.

3.4 Ethical Consideration

The proposal for this study was presented to the Research and Ethical Committee of Jos University Teaching Hospital for approval. Informed consent was obtained from the subjects before enlistment into the study.

3.5 Sample Size

The sample size estimation was calculated using the formula for studying proportions with population >10,000 i.e. $N=Z^2pq/d^2$ in Araoye[67]:

$N=z^2 pq/d^2$

N= desired sample size

Z=standard normal deviate 1.96 which correspond to 95% confidence interval.

P= prevalence expressed as 100% i.e 12%[22]

q=complimentary proportion 1-p
d=degree of accuracy desired=0.05

$$N=\frac{(1.96)^2 \times 0.12 \times 0.88}{(0.05)^2}$$

161.4532

A total of 167 pregnant women were recruited in the Study (none or once SP) group and 171 in the Control (twice SP) group.

3.6 Data Collection

Collection of Blood Samples

3mls of blood samples were collected aseptically by venepuncture using 5 ml sterile disposable hypodermic syringes and needles before delivery in labour ward and dispensed into prelabelled EDTA specimen bottles and transferred to the medical microbiology laboratory of the hospital.

Maternal blood samples were also collected into heparinised microhaematocrit tubes, sealed and spurned at 12000 revolutions per minute for 5minutes using a haematocrit centrifuge(Hawskey and Sons Lancing UK) at the haematology laboratory of the JUTH. The packed cell volume was read off as percentages using a Hawskey haematocrit tube reader.

Thick blood smears were prepared and examined at medical microbiology laboratory. Blood smears were stained using Giemsa stain and parasites were counted against 100 leukocytes and expressed as number of parasites/ml of blood assuming a standard leukocyte count of 8000/ml of blood. A blood smear was negative when minimum of 100 high power fields was examined with no parasites seen.

Parasite density was calculated as mean geometric mean parasite density (GMPD/ml).

Placental blood was collected within an hour after child-birth, by incising the cleaned maternal surface (basal plate) of the placenta and drawing 5ml of blood welling from the incision using a sterile syringe and needle. Thick blood film was prepared, stained with Giemsa stain and also analyzed according to the procedure for microscopic diagnosis for malaria parasitaemia.

Quality control was ensured by re-examination of a randomly selected 10% sample of all slides by another Scientist to confirm the accuracy of the results.

Sample collection was done by the researcher with assistance from some Resident Doctors and House Officers in the Department. The test was carried out by 2 experienced Laboratory Scientists. One is a Haematologist and the other a Microbiologist. Samples were sent to the laboratory as they were collected and the researcher supervised each and every analysis.

3.7 Statistical Method for Data Analysis

The comparisons were made using means or chi square test. Chi square was used to determine significance of association between categorical data. Continuous independent variables like birth weight were tested using analysis of variance (ANOVA). P value of < 0.05 was considered statistically significant in all statistical comparisons .All analyses were conducted using the SPSS version 15 software.

3.8 Limitation to the Study

Apart from malaria in pregnancy, there are other risk factors for anaemia that may not be easy to control in this study. These include difficulty in assessing nutritional status of participants, difficulty in assessing precisely the socio-economic status of participants and also difficulty in assessing contributions by other factors like hookworm etc.

Also inability to test for placental malaria parasitaemia using histological methods, which is the gold standard, is another limitation. Histology was not used for diagnosis in this case because of the huge cost implication

3.9 Benefits of the Study

To the Patient

1. Opportunity to have their pack cell volume and malaria parasite test done at no cost to the participant.

To Humanity

Efficacy or otherwise of current policy on Intermittent Preventive Therapy would have been proven and this would affect further policy decisions.

RESULTS

Table 1: **Mean age, weight, height and booking PCV.**

Characteristics	None or 1 SP	Twice SP	P- value
Mean age (years)	28.41±5.5	29.83±5.8	0.022 *
Mean weight (Kg)	75.83±46.87	77.71±43.17	0.700
Mean height (cm)	160.31±6.00	159.69±7.40	0.403
Booking PCV (%)	33.84±2.82	34.26±2.76	0.204

*Statistically significant.

Table 2: Social Class

Participant's level of education	**None or once SP**	**Twice SP**
Primary	13	13
Secondary	87	63
Tertiary	63	92
None	4	3
Total	**167**	**171**
Participant's occupation	**None or once SP**	**Twice SP**
Civil/public servant	39	59
Business woman	26	37
House wives	61	40
Hair dresser	17	14
Students/ NYSC	21	20
Missionary	3	1
Total	**167**	**171**
Husband's level of education	**None or once SP**	**Twice SP**
Primary	8	10
Secondary	83	43
Tertiary	76	116
None	0	2
Total	**167**	**171**
Husband's occupation	**None or once SP**	**Twice SP**
Artisan	17	19
Business man	50	54
Civil / public servant	86	90
Student / NYSC	9	3
Farmer	0	4
Missionary	2	1
Unemployed	2	0
Total	**166**	**171**
Social classification(Olusanya et al [68])	**None or once SP**	**Twice SP**
Social class 1	2	6
Social class 11	77	75
Social class 111	66	69
Social class 1V	21	19
Social class V	1	2
Total	**167**	**171**

No statistically significant association between the study group and social classification. X^2=3.790, P value=0.876.

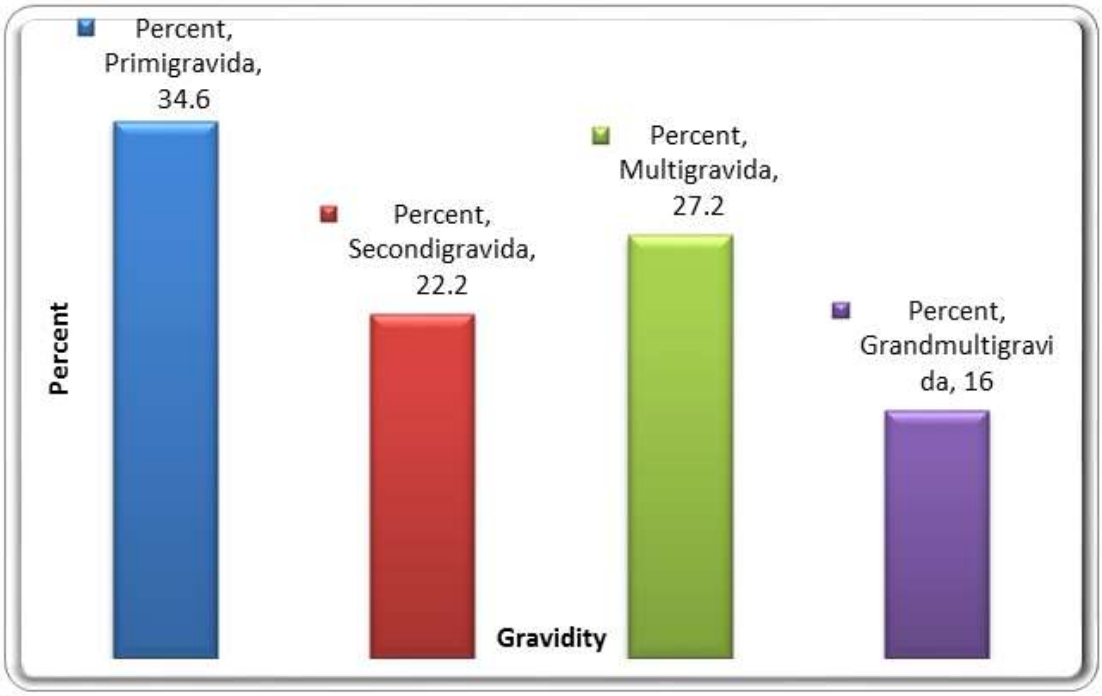

Figure 1. Distribution of General Subjects by Gravidity

Primigravidae=1st pregnancy, secundigravidae=2nd pregnancy, multigravidae=3rd and 4th pregnancies and grandmultigravidae=5th and above
X^2=9.407, L.R= 9.571, P value=0.024

Table 3: Malaria treatment in index pregnancy and parasite density

Treatment	-	+	++	+++	Total
Yes	30 (34.9%)	52 (60.5%)	2 (2.3%)	2 (2.3%)	86 (100.0%)
No	108 (42.9%)	130 (51.6%)	14 (5.6%)	0 (0.0%)	252 (100.0%)
Total	138 (40.8%)	182 (53.8%)	16 (4.7%)	2 (0.6%)	338 (100.0%)

X^2=9.211, P value=0.027

Table 4: Use of insecticide treated nets and maternal peripheral parasitaemia.

Use of ITN_S	Positive MP	Negative MP	Malaria pigments	Total
Yes	95 (56.5%)	49 (29.2%)	24 (14.3%)	168 (100.0%)
No	106 (63.9%)	38 (22.9%)	22 (13.3%)	166 (100.0%)
Total	201 (60.2%)	87 (26.0%)	46 (13.8%)	334 (100.0%)

No association between use of ITN_S and placental malaria parasitisation; X^2 =5.555 P value= 0.135

Table 5: Maternal peripheral malaria parasitaemia

Study Groups	Positive MP	Negative MP	Pigments	Total
None or once SP	126 (75.4%)	25 (15.0%)	16 (9.6%)	167 (100.0%)
Twice SP	75 (44.9%)	62 (37.1%)	30 (18.0%)	167 (100.0%)
Total	201 (60.2%)	87 (26.0%)	46 (13.8%)	334 (100.0%)

$X^{2=}$32.937 P Value= 0.000.

Table 6: Species types involved

Study Groups	P. falciparium	P. malariae	P. Ovale	P. vivax	Total
None or once SP	74 (59.2%)	47 (37.6%)	2(1.6%)	2(1.6%)	**125**(100.0%)
Twice SP	53 (71.6%)	19 (25.7%)	0(0.0%)	2(2.7%)	**74**(100.0%)
Total	**127** (63.8%)	**66**(33.2%)	**2**(1.0%)	**4**(2.0%)	**199**(100.0%)

Table 7: prevalence of anaemia
(Using PCV<30% and PCV<33%)

Study Groups	PCV<33% (anaemic)	PCV <33 (not anaemic)	PCV <30% (anaemic)	PCV <30% (not anaemic)	Total PCV <33%	Total PCV <30%
None or Once SP	14 (8.4%)	153 (91.6%)	1 (0.6%)	166 (99.4%)	167 (100.0%)	167 (100.0%)
Twice SP	10 (5.8%)	161 (94.2%)	4 (2.33%)	167 (97.67%)	171 (100.0%)	171 (100.0%)
Total	**24 (7.1%)**	**314 (92.9%)**	**5 (1.5%)**	**333 (98.5%)**	**338 (100%)**	**338 (%)**

P Value=0.403 (Fisher exact test)-PCV<33%
P Value=0.4655 (Fisher exact test)-PCV<30%

Table 8a: birth weight of babies in the two groups.LBW= <2500kg

Study Group	LBW	Normal weight	Total	Mean weight of babies(g)
None or once SP	5 (3.0%)	162 (97.0%)	167 (100.0%)	3120.6±44.76
Twice SP	0 (0.0%)	171 (100.0%)	171 (100.0%)	3255.4±463.17
Total	5 (1.5%)	333 (98.5%)	338 (100.0%)	

Statistically significant difference in low birth weight LBW in the two groups
X^2= 5.197, P Value (using fisher exact test) = 0.029,
Also in mean weight of babies, p value= 0.0066

Table 8b: Placenta parasitisation in the two groups

Study Group	-ve	P.G	+	++	Total
None or once SP	38 (22.9%)	21 (12.7%)	99 (59.6%)	8 (4.8%)	166 (100.0%)
Twice SP	69 (40.4%)	40 (23.4%)	62 (36.3%)	0 (0.0%)	171 (100.0%)
Total	107 (31.8%)	61 (18.1%)	161(47.8%)	8 (2.4%)	337 (100.0%)

X^2 =31.335 P Value=0.000,

4. DISCUSSION

The study was undertaken to find out if there are statistically significant differences in the prevalence of malaria parasitaemia, anaemia, low birth weight and placental parasitisation between pregnant women who took 2 doses of SP and those that had none or once SP

Social classification of the two groups were done using protocol for social classification by Olusanya et al (1985), social classes 1-V were derived using the husband's occupation and the wife's education[68]. There was no statistically significant association between the social class in the two groups. Also social class did not significantly affect the anaemia, maternal malaria parasitaemia and the placental parasitaemia. P values were > 0.05. But the protocol did not address the women that had no formal education and also who qualifies as 'middle level' in the husband's occupation was not easy to determine

In the none or once SP study arm, there were 167 women, out of whom 75.4% had positive MP, 9.6% had pigments and 15% were negative. While in the twice SP control group, of the 167 women, 44.9% had positive MP, 18% had pigments and 37.1% were negative. This was statistically significant. X^2=32.937, P value=0.000 Likelihood Ratio=33.660,

The prevalence of malaria parasitaemia in the twice SP study arm is comparable to 45% prevalence rate reported by Praise et al (1998) in Kenya in which SP or chloroquine was used as intermittent presumptive treatment[5]. Also in an observational study in Malawi, Sullivan et al (1999) also found a prevalence of 37% malaria parasitaemia.

A cross sectional study carried out at University of Maiduguri Teaching Hospital by Bako et al (2009) found a prevalence of 30.7 in the subjects. 68% of the subjects had used 2 doses of SP[25]. The reported prevalence in the above study is lower than observed in the two-study arms in this particular study. These are geographically distinct population. Here difference in geographical location and difference in the uptake of insecticide treated nets could account for the difference. Jos is on the plateau at an altitude of 1,200m above the sea level[26]. The inverse relationship between malaria prevalence and altitude has been reported elsewhere in Tanzania. In a study in Usambra mountain in the North eastern Tanzania, a prevalence of malaria in children was observed to decrease by 5% for every 100m increase in altitude from 82% in the lowlands (300m) to 12% in the highlands (1700m)[69]. It was supported by another study also in Northern Tanzania[70]. Lower malaria prevalence in higher altitude is likely to be attributed to low ambient temperatures that discourage vector transmission[71]. However, local variations in seasonality of malaria transmission including vector species composition, topography, host and parasite genetics and socioeconomic factors influence the prevalence of malaria parasitaemia in any given area[71].

Nnatu et al (1987) in a Lagos cross-sectional study of 230 women at delivery reported a prevalence of 40%[72]. Here details of antimalarials and malaria chemoprophylaxis were not given hence the data were difficult to compare.

Ogbodo et al (2009) reported a prevalence of 59.9% in a cross sectional study involving 272 women in a rural community in Ebonyi State, where a case was made for the need for combined preventive approach[19]. Prevalence rates are comparable

The prevalence of anaemia in the two groups show that out of the 167 in the none or once SP arm 14 (8.4%) had PCV less than 33% while in the twice SP arm, out of the total of 171 women, 10 (5.8%) had PCV less than 33%. It is true that the prevalence of anaemia is higher in the none or once SP. However this did not reach a statistically significant level. X^2=0.823, L.R= 0.826, P value=0.364.

The difference was not also statistically significant when PCV less than 30% was used as cut-off for anaemia. Using Fisher exact test, P value = 0.4655, Risk Ratio 0.506, C.I= 0.353-2.366.

The prevalence of anaemia in the study arm and control arm are lower than most reported prevalence rates locally[73] and regionally[74]. But prevalence rate 2-30% has also been reported[75]. Difference in nutritional status, hookworm and schistosomiasis infestations could account for the differences. Moreover in this study, women with risk factors known to be associated with anaemia such as sickle cell disease, multiple

pregnancies, women with severe preeclampsia, women who are not compliant on haematinics were excluded from the study.

The prevalence of low birth weight (LBW) in the two groups when also compared showed that of the 167 women in the none or once SP study, 5 had LBW giving a prevalence of 3%. But there was no recorded case of LBW of the 171 women in twice SP control arm. This was statistically significant. X^2= 5.197, L.R = 7.127, using Fisher exact test, P value=0.029

When the mean birth weights in the two groups were compared, the none or once SP group was 3120.5988 while the twice SP group was 3255.4035. Again this was statistically significant. T stastistic=2.7341, P value=0.0066.

Prevalence of LBW of 9.5% after 2 doses of SP as against 13.3% in group that had no intervention was reported by reported Challis et al (20004), in a randomized control trial in southern Mozambique[76]. Difference could be accounted for by sample size and difference in other determinant of final birth weights like race, maternal weight, paternal height, and other medical conditions associated with LBW, most were excluded from this study.

Also prevalence of LBW of 8% was also reported in similar cross sectional study in Maiduguri[25]. This particular study also found a statistically significant association between placental parasitisation and LBW. In this study, all the 5 babies with LBW had placenta malaria parasitisation. The high perfusion of human placenta makes it easily accessible to malaria parasites in the maternal circulation making placenta malaria a common finding[25].

Placenta malaria parasitisation in the two groups also showed interesting results. Of the 166 in the none or once SP group 38 (22.9%) was negative, 21 (12.7%) had pigments and 99 (59.6%) had 1+, with 8 (4.8%) having 2++. In the twice SP control arm, of the 171 women, 69 (40.4%) was negative, 40 (23.4%) had pigments, 62 (36.3%) had 1+. There was none in this group with 2++. This was statistically significant. X^2=31.33, L.R= 34.725, P value=0.000. Also of the 61 placenta blood with malaria pigments which suggests previous infection, 40 were in the twice SP group while 21 were in none or once SP group showing that 2 doses of SP in pregnancy is more effective in the placenta malaria parasite clearance. X^2=6.684, L.R=6.783, Using Fisher exact test, P value =0.011.other authors also agree that IPT with SP is effective in reducing placenta malaria in our environment[77].

The prevalence of placenta parasitisation is however higher than that reported by Bako et al (2009) where a prevalence of 33.9% was reported[25]. Also Ukaga et al(2007) in a multicentre cross sectional study in Owerri Imo State South eastern Nigeria found a placental parasitisation of 29.9%[78]. The difference could be accounted for by study population, malaria transmission, or differences in diagnostic methods. Placental malaria prevalence of 57.69% was reported by Ibhanesebhor and Okolo (1992) in Benin which is comparable to the prevalence in the none or once SP study arm[79]. Though there was no intervention in the form of either IPT or ITN_S in the Benin study.

5. CONCLUSION

The results of the study showed that there was statistically significant higher prevalence of maternal malaria parasitaemia in the none or once SP study group compared to twice SP control group

It also showed that the prevalence of anaemia before delivery was higher in the none or once SP study group compared to twice SP control group. But this was not statistically significant

There was also statistically significant higher prevalence of malaria parasitisation in the none or once SP study group compared to twice SP control group

It also showed that there was statistically significant higher prevalence of low birth weight LBW in the none or once SP study group compared to twice SP control group

It also showed that there was statistically significant higher prevalence of Placental parasitisation in the none or once SP study group compared to twice SP control group

Recommendation.

Following this study, it is recommended that:

1. Effort toward improving the uptake of at 2 doses of SP should be improved upon through health education of both patient and health care givers at all levels of care.
2. The DOT system for the administration of SP should be resuscitated, thereby curbing the occurrence of non-compliance by patients
3. Monitoring and supervision of the IPT programme implementation should be stepped up at all levels of health care delivery. This will among others ensure not only that the drugs are available for administration but also that they are administered to the patient. .

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APPENDIX

APPENDIX A

CONSENT FORM

I, Dr. Ozele, Kingsley Chukwuka of the Department of Obstetrics and Gynaecology, JUTH, wish to carry out a research on anaemia in pregnancy (low blood level) and malaria parasitaemia (malaria parasite in the blood) in women at delivery after 2 doses of sulfadoxine-pyrimethamine combination (fansidar) at the Jos University Teaching Hospital, Jos, Plateau State.

Before you decide if you would like to take part or not, please read the following carefully.

WHAT IS THE STUDY ABOUT?

The study is aimed at finding out how effective intermittent preventive therapy using sulphadoxine-pyrimethamine in reducing anaemia in pregnancy and malaria parasitemia

WHAT WILL BE DONE TO YOU IF YOU PARTICIPATE IN THIS STUDY?

About 5mls of blood will be collected from your vein and taken to the laboratory and analysed for malaria parasites and to know your blood level (pack cell volume)

WILL THE INFORMATION BE CONFIDENTIAL? YES

The information collected during this study will be stored and analysed without including your name. Only your Doctors will know that the information is related to you. The results of the study may be published in medical literature but your identity will not be revealed.

WRITTEN CONSENT FORM

I…… (Initials please) have read and understood all the information given to me about my participation in this study and I have been given the opportunity to discuss it and ask questions. All my questions have been answered to my satisfaction and I voluntarily agree to take part in this study. I understand that I will receive a copy of this signed written informed consent form. I authorize the release of my medical records to the investigator, regulatory authorities and ethical committee as may be required.

Signature / thumb print of subject ……Date……
Initials of subject ……
Signature / thumb print of witness ……Date……..
Initials of witness ……..
Signature of investigator …… Date……
Initials of investigator …….

APPENDIX B
PRO FORMA

ANAEMIA IN PREGNANCY AND MALARIA PARASITAEMIA IN WOMEN AT DELIVERY AFTER 2 DOSES OF SULFADOXINE-PYRIMETHAMINE COMBINATION AT THE JOS UNIVERSITY TEACHING HOSPITAL, JOS, PLATEAU STATE

1. Serial No ……..
2. Date……..
3. Hospital No ……..
4. Age (years) ……

5. Ethnicity (a) Hausa/Fulani (b)Igbo (c)Yoruba
(d) Others (specify) …….

6. Place of residence……..
7. Level of education (a) none (b) primary (c) secondary (d) tertiary

8. Occupation (a) housewife (b) student (c) trader (d) self employed
(e) Civil servant (specify) …….

9. Husband's level of education (a) none (b) primary (c) secondary (d) tertiary

10. Husband's occupation (a) unemployed (b) student (c) trader
(d) Self employed (e) civil servant (specify) …….

11. Parity…….
12. Gestational age at delivery (weeks)……
13. Maternal height……
14. Maternal weight in labour. ……..
15. When last did you take a worm expeller?

Section 2

Treated for malaria in this pregnancy? Yes ….NO……..
If yes how many times …….
What was used in treatment……..
Sleep under insecticide treated net? ……..

Section 3

Maternal packed cell volume…….
Maternal malaria parasitaemia ……
Maternal malaria parasite density…….
Maternal malaria parasite species……
Placenta malaria parasitaemia.....

Section 4

Weight of baby …….
Weight of placenta……

WORK PLAN

30th October, 2009: Passed Part 1 Fellowship examination of the West African College of Surgeons, Faculty of Obstetrics and Gynaecology.
April 2010: Dissertation topic selected .Supervisors given drafts of proposal for inputs and correction
June 2010: Proposal sent to JUTH ethical committee for clearance/approval
3rd August, 2010: Approval from JUTH Ethical Committee

15th September, 2010: Dissertation proposal sent to the College
15th January, 2011: Dissertation proposal received from College. Accepted with major revision
April 2011: Corrected copy sent back to the College
June 2011 to December 2011: Sample and Data collection and analysis of data:
April 2012: Proposed date for Part 11 Fellowship Examination