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Original

Placental Malaria Parasitemia and Pregnancy Outcome in Two Secondary Health Facilities in Abuja

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ABSTRACT

Introduction: Placental malaria is a distinct feature of malaria in pregnancy which occurs as a result of sequestration of plasmodium falciparum parasites in the placenta. It has been associated with adverse consequences to the mother, fetus and neonate especially in areas of high endemicity. This study was conducted to determine the relationship between Placental Malaria and maternal anemia, neonatal anemia, birth weight and congenital malaria at parturition. **Methodology:** A Cross-sectional study which involved 210 eligible parturients in labor was carried out over a 6-month period in two secondary health facilities in Abuja. Maternal blood was taken for Malaria Parasite (MP) and packed cell volume (PCV) prior to delivery. Cord blood was also collected for MP and PCV while placental blood was examined for MP. The weight of the neonate was measured at delivery. Statistical analysis of the data was done and the level of statistical significance was set at a probability value of less than 0.05 ($P < 0.05$). **Results:** Cord parasitemia (congenital malaria) was found to be significantly higher in those with placental parasitemia. Placental parasitemia was also associated with low birth weight (P=0.0001). There was no statistically significant relationship observed between placental parasitemia and maternal anemia (P=0.904) or fetal anemia (P=0.669). **Conclusion:** Placental malaria is associated with low birth weight and congenital malaria both of which have extensive adverse effects on pregnancy outcome. Pre-emptive measures should be ensured in pregnant women to mitigate these negative impacts.

Keywords: Placental malaria, Birthweight, congenital malaria, Maternal Anemia

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INTRODUCTION

Malaria is a major health concern worldwide. It causes 300–500 million infections and approximately 1.1–2.7 million deaths annually.[1] Every year, 30 million women susceptible to malaria become pregnant in Africa, with about 10,000 maternal mortalities attributed to the disease and up to 200,000 newborn deaths annually.[2,3] Malaria contributes an estimated 11% to maternal mortality in Nigeria.[4] The Increased vulnerability of women to this infection while pregnant increases risk of negative pregnancy outcome including spontaneous miscarriages, preterm delivery, still birth, low birthweight and perinatal mortality.[5,6] Malaria is also associated with maternal severe anemia, maternal hypoglycemia, acute pulmonary edema, cerebral

edema, renal failure, puerperal sepsis, postpartum hemorrhage and increased risk of death.[1,7,8]

The adverse consequences in pregnancy are mainly as a result of sequestration of parasitized erythrocytes present in the placental intervillous spaces. Placenta parasitemia incite release of inflammatory mediators, which affect placental function thus accounting for the adverse fetal outcome.[6,9] This sequestration in the placenta is a virulent factor exclusively displayed by *Plasmodium falciparum (P.falciparum)* and not by other human malaria parasites.[6] Placental isolations of *P.falciparum* also occur in the absence of parasite detection by microscopy in maternal peripheral blood during sub-microscopic infection.[5] It may sometimes exceed 50% of placental erythrocyte without any parasite in the peripheral blood.[8] The Parasitized red blood cells express *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) on their surface, mediating cytoadhesion to endothelial cells, platelets, erythrocytes and syncytiotrophoblast, thereby evading circulation and destruction in the spleen.[10] Variant Cell surface antigen (VAR2CSA), a unique member of the PfEMP1 protein family helps parasitized red blood cells adhere to the adhesion molecule Chondroitin sulfate A (CSA) receptors in the placental syncytiotrophoblast which provides an ideal environment for the seclusion of parasite-infected red blood cells. [10]

The World Health Organization (WHO) has recommended a three-prong approach to the prevention and control of malaria during pregnancy in areas of stable transmission. This includes the use of intermittent preventive treatment (IPT) of asymptomatic pregnant women, use of insecticide treated nets (ITNs) and prompt and effective case management of both complicated and uncomplicated cases of malaria in pregnancy.[6,9,11] Despite adequate chemoprevention, placental malaria still occurs and gives rise to adverse pregnancy outcomes because of sequestration of the malaria parasite in the placenta bed.[9] These adverse outcomes have far reaching consequences when they occur. Low birth weight is the single most important risk factor for neonatal and infant mortality.[3] It is also a well-documented risk factor for poor neuro-sensory, cognitive and behavioral development, as well as for limited school performance and academic achievement.[3] Congenital malaria can make the newborn more susceptible to immunologically mediated hemolysis or to dyserythropoiesis.[12] These consequences make it a necessity to understand how placental malaria specifically affects pregnancy outcomes and is crucial in efforts to improve maternal and perinatal health and curb the spread of this preventable infectious disease.[13]

Justification

Placental malaria parasitemia though extensively researched, remains a significant source of concern in hyper-endemic areas like the study area where the disease burden is ever increasing with attendant adverse pregnancy outcomes. These outcomes have consequences that persist beyond the perinatal period. Thus, more studies that update prevalent data and information on the subject matter remain relevant in ongoing efforts to improve pregnancy outcomes especially in the study region where there is a paucity of such studies.

MATERIALS AND METHOD

The study was carried out in the labor wards of both Garki and NISA Premier Hospitals in Abuja (Garki-Nisa Hospital). Garki Hospital Abuja (GHA) is a public private partnership with the Federal Capital Territory Authority (FCTA) that started in March 2007 and was incorporated into the NISA premier group of hospitals. They are both secondary health facilities that provide specialized healthcare and serve as referral centers for patients within the Federal Capital Territory (FCT) and its environs. The labour wards of both hospitals have an average of 2000 deliveries every year.

The study was Cross-sectional in design and carried out over 6 months. It included all consenting parturients who had deliveries conducted in the labor wards of both Hospitals during the study period and excluded those with chronic medical disorders including diabetes mellitus, hypertension, chronic renal disease, sickle cell anemia and Human immunodeficiency virus (HIV) infection. Women who used tobacco products and recreational drugs, those with antepartum hemorrhage, multiple gestation, intrauterine fetal death or congenital fetal malformations were also excluded.

Using a prevalence rate of 14.2% from a previous study [14] the sample size (N) needed to achieve a precision of 5% at 95% confidence interval was obtained using the formula below;

$N = Z^2 P(1-P)/d^2$ where Z = 1.96 P = 0.142 and d = 0.05

The sample size thus calculated was 187. Giving allowance for a 10% attrition rate, the minimum sample size for the study was 210 participants.
On Arrival in the labor ward, the eligible participants were recruited and assigned a study code number. A pretested semi-structured interviewer-administered questionnaire was used for data collection. The questionnaire contained details that included maternal age, marital status, educational status, gravidity, gestational age at delivery, booking status and malaria preventive measures used in index pregnancy. The post-delivery information which included infant birth weight, maternal and neonatal hematocrit, neonatal, maternal and placental blood microscopy for malaria parasite detection was filled in the questionnaire after delivery and analysis of the sample.

Three milliliters of maternal peripheral blood (labelled M-study code number) and cord blood (labelled C-study code number) was taken in an EDTA bottle for estimation of packed cell volume (PCV) and blood film for Malaria parasites. Three milliliters of placental blood (labelled P-study code number) was collected using the placental prick method [15] and assessed for malaria parasites.

Slides with frosted ends were labelled appropriately and used to make blood smears. A drop of the blood sample was placed at the center of a slide using a Pasteur pipette. The corner of a second slide was used to spread the drop of blood in a circular manner to make a thick smear and allowed to air-dry. A drop of the blood sample was placed close to the frosted end of another slide. The edge of a second (Spreader) slide was used to touch the drop of blood and allow it to extend along the edge of the spreader. The spreader slide was then held at about a 30-degree angle and used to spread the blood towards the unfrosted end of the slide to make a thin film. The film was allowed to air dry on a staining rack for about 10 minutes and fixed by adding 1-2 drops of absolute Methanol. Both slides were then immersed in a staining trough, containing 10% of freshly prepared Giemsa solution at pH 7.2 and left inside for 10 minutes to allow for proper staining. The slides were then removed and placed in a water trough containing water for 3-5 mins after which they were removed and placed vertically in a slide draining rack to dry.

The blood smears were examined under × 100 oil immersion lens of a light microscope. Malaria diagnosis was based on identification and count of asexual stages of Plasmodium species on the thick blood smear while the thin blood smear was used for species identification.

Parasite density was determined by counting the number of parasites per high power field (hpf) in the thick blood smear and reported as follows: + (1–10 parasites per 100hpf), ++ (11 – 100 parasites per 100 high power fields), +++ (1–10 parasites per hpf), and ++++ (>10 parasites per high power field).

The slide was reported as negative if no parasite was identified per 100 high power fields. For quality assurance, ten slides were randomly selected every month during the study period to be examined by another microbiologist and results compared with that obtained by the research microbiologist.

For PCV estimation, the hematocrit capillary tube was filled to three quarter level, sealed with plasticine and placed in a micro hematocrit centrifuge (Hawksley Haematospin 1400). The centrifuge was set to spin the sample at 3000 revolutions per minute for ten minutes. The PCV was then obtained by placing the capillary tube in the tube holder of the Hawksley microhematocrit reader. In this study, Anemia was defined as Maternal PCV <30% and Neonatal PCV <37.5%.

Neonates were cleaned and weighed at delivery. Weights less than 2500 kg were classified as low birth weight.

Data Analysis

Data obtained were entered and statistical analysis was done using statistical software (SPSS for windows® version 22.0, SPSS Inc.; Chicago, USA). Results of descriptive statistical analyses are presented on tables with counts and percentages, while inferential statistics; Chi-squared test for categorical relationships, T-test for differences in mean and multivariate logistics regression analysis for causal effects were performed. The decision rule for inferential statistical significance was considered at $p<0.05$.

Ethical Consideration

Ethical clearance was obtained from the Health Research and Ethics Committee of Garki-Nisa hospital, Abuja. Participation was voluntary. The nature and objectives of the study was explained to each participant and consent obtained from them before enrollment in the study. Participants were not responsible for funding the tests. Participants had the right to withdraw from the

study whenever they deemed fit. Confidentiality was maintained by identifying patients with a study code.

RESULTS

A total number of 210 women participated in the study with a 100% response rate. Their ages ranged from 19 to 42 years with a mean age of 29.4±4.9 years. The modal age group was 30-39 years which made up 48.6% of the study population as shown in Table 1. The participants were predominantly married women (98.6%) with tertiary level (84.3%) of education.

Majority of the participants (55.2%) were multiparous. Two hundred and four (97.1%) parturients were booked while 6 (2.9%) were unbooked. The 204 booked participants had at least four antenatal clinic visits while the 6 parturients who had none corresponded to the unbooked participants. The average gestational age at delivery was 38.5±1.2 weeks (Range = 36-42 weeks); of these, 99% of the parturients delivered at term, while only 1% were preterm.

Table 1: Maternal Socio-demographic Profile

Variable	Mean ± SD	Frequency N (%)
Age (years) Mean ± SD	29.4±4.9	
Age Group		
<20		3(1.4)
20-29		99(47.1)
30-39		102(48.6)
≥40		6(2.9)
Educational status		
None		3(1.4)
Primary		3(1.4)
Secondary		27(12.9)
Tertiary		177(84.3)
Marital status		
Single		3(1.4)
Married		207(98.6)
Religion		
Christian		120(57.1)
Islam		90(42.9)
Tribe		
Hausa		96(45.7)
Igbo		37(17.6)
Yoruba		42(20.0)
Others		35(16.7)

Table 1: Obstetrics Factors and Delivery Outcomes

Variable	Mean ± SD	Frequency N (%)
Parity	1.9 ±1.3	
Nullipara/Primipara		85(40.5)
Multipara		116(55.2)
Grand Multipara		9(4.3)
Number of ANC Visits		
0		6(2.9)
≥ 4		204(97.1)
Booking status		
Booked		204(97.1)
Unbooked		6(2.9)
Gestational age at delivery in weeks (Mean ± SD)	38.5 ±1.2	
Delivery outcome		
Average birthwieght	3128.5 ± 405.1	
Normal birth wieght (2500-3999g)		182 (86.7)
Low birth weight (< 2500 g)	Term=26 Preterm=-2	28(13.3)
Preterm delivery (< 37 weeks of gestation)		2(1.0)
APGAR score at 1st minute (Mean ± SD)	8.6±0.2	
APGAR score at 5th minute (Mean ± SD)	9.7±0.5	
Average placental weight	432.5±58.1	

Table 3: Malaria control measures

Parameter	N (%)
Use of IPT (Sulfadoxine-Pyrimethamine)	
0	8(3.8)
2	3(1.4)
3	199(94.8)
Arthemeter/Lumefantrine	
0	165(78.6)
1	27(12.9)
2	18(8.6)
IV Artesuate	
0	195(92.9)
1	15(7.1)
Use of ITN	
No	168(80.0)
Yes	42(20.0)
Have door and/or window nets at home	
No	11(5.2)
Yes	199(94.8)
Use of insecticide sprays	
Less than once a week	181(86.2)
Once a week	9(4.3)
Twice A Week or More	11(5.2)
Does Not Use	9(4.3)
Use of mosquito coils	
Once A Week	6(2.9)
Does Not Use	204(97.1)

Table 4: Prevalence of placenta parasitaemia, peripheral parasitaemia and cord parasitaemia

Variable	N (%)
Placenta parasitaemia	
Negative	167(79.5)
Positive	43(20.5)
Peripheral parasitaemia	
Negative	180(85.7)
Positive	30(14.3)
Cord parasitaemia	
Negative	172(81.9)
Positive	38(18.1)

Table 5: Association between placenta parasitemia and Peripheral (maternal) and cord parasitaemia

Parameter	Placenta parasitaemia		Relative Risk(RR) (95% CI)	p-value
	Positive	Negative		
	N (%)	N (%)		
Peripheral parasitaemia				
Positive	26 (12.4)	4(1.9)	9.2	0.0001
Negative	17(8.1)	163(77.6)		
Congenital parasitaemia				
Positive	35(16.7)	3(1.4)	19.8	0.0001
Negative	8(3.8)	164(78.1)		

Table 6: Relationship between placenta parasitemia and maternal and neonatal anaemia

Parameter	Placenta parasitemia		Independent t-test	p-value
	Positive Mean ± SD	Negative Mean ± SD		
Maternal anaemia (PCV < 30%)	(n = 13)	(n = 2)		
	28.5 ± 0.7	28.5 ± 0.7	0.08	0.904
Neonatal anaemia (PCV < 37.5%)	(n = 31)	(n = 2)	0.44	0.669
	35.5 ± 1.2	35.9 ± 1.2		

Table 7: Association between placenta parasitaemia and parity, age at delivery and birthweight

Parameter	Placenta parasitaemia		Test of statistics	P
	Negative N (%)	Positive N (%)		
Parity			Chi square (χ^2) 42.6	**0.0001**
Nullipara/Primipara	49 (23.3)	36 (17.1)		
Multipara	109 (51.9)	7 (3.3)		
Grand multipara	9 (4.3)	0 (0.0)		
Maturity at delivery			Chi Square (χ^2) 7.84	**0.005**
Preterm (GA < 37 weeks)	0 (0.0)	2 (1.0)		
Term (GA ≥ 37 weeks)	167(79.5)	41 (19.5)		
Birth weight (g) [Mean ± SD]	3265.6 ± 287	2596.0 ± 352.3	Independent t-test 12.9	**0.0001**
Low birth weight (< 2500 g)	3 (1.4)	25 (11.9)	Chi square (χ^2) 93.4	**0.0001**
Normal birth weight (2500- 3999 g)	164 (78.1)	18 (8.6)		

The mean infant birth weight was 3128.5±405.1 grams. The babies with normal birth weight were 182 (86.7%) while 28 (13.3%) babies had low birth weight. Of the low-birth-weight babies, 2 were preterm babies while 26 were term low birth weight babies. The APGAR score at the first and fifth minutes of life were normal (≥7) for all the neonates and the average placental weight was 432.5±58.1grams.

Malaria control measures adopted by the participants were Intermittent preventive treatment with Sulphadoxine-Pyrimethamine IPTpSP (96.2% of the participants) and 94.8% had three doses. Only 20% of the participants slept under Insecticide treated nets (ITNs) (Figure 5.3) However, (94.8%), had window and door nets. Indoor residual spraying was done by 4.3% at least once a week and 2.9% of the participants used mosquito coils. Sixty (28.6%) participants were treated for symptomatic malaria during pregnancy. Arthemeter-Lumefantrine combination was the most common antimalarial used by 21.5% of the participants.

The prevalence of placental, peripheral and cord malaria parasitaemia among the parturients is presented on Table 4 and reveals that placenta malaria parasitaemia was present in 20.5% of the participants, 14.3% had peripheral (maternal) malaria parasitaemia and the prevalaence of Cord parasitaemia (congenital malaria) was 18.1%.

Table 5 shows that the relationship between placenta parasitemia and maternal and neonatal (cord) parasitaemia are statistically significant, but there is a stronger relationship between placenta parasitemia and neonatal (cord) parasitemia with a higher relative risk (RR = 19.8).

Table 6 shows that of the 210 participants, 15 had peripheral (maternal) anaemia and 13 of these were also positive for placental parasitaemia. Neonatal anaemia was observed in 33 participants and 2 of these were negative for Placental parasitaemia. From these, no statistically significant relationships were obtained between placenta parasitemia and maternal and neonatal anaemia.

Association between placenta parasitemia and birth weight

Table 5.8 shows that there was a reduction in birthweight in neonates who had placental malaria parasitaemia. The association of placental parasitaemia with low birth weight was found to be statistically significant with a P – value of <0.0001. There was also a reduction in average birthweight in those who were positive for placental malaria parasitaemia compared to those who were not.

DISCUSSION

The overall prevalence of placental malaria parasitaemia in this study was 20.5%. This is similar to the prevalence of 18.2% observed in Uyo, [5] and 19% recorded in Abeokuta,[18] South west Nigeria. A much higher prevalence of 65.2% and 59.3% was observed in Port Harcourt [9] and Sudan [16] respectively. The disparities in prevalence in different studies may be as a result of variations in case selection, community acquired immunity, quality of antenatal care, resistance to antimalarial drugs and diagnostic tools employed for parasite detection.[9,17]

A contributing factor to the low prevalence observed in this study could be the utilization of malaria chemoprophylaxis with sulphadoxine-pyrimethamine (IPTp-SP) which was very high among the study population (96.2%). The recommended three doses [17] of IPT-SP was received by 94.8% of the participants and this has been shown to give more protection from placental parasitaemia than only two doses in a study done in Bayelsa.[17]

The high utilization could be attributed to the good health seeking behavior of the study participants who mostly had tertiary level of education (84.3%) and also the availability of liquid formulation of the medication which are sometimes administered as directly observed therapy (DOTS) in the study hospitals. The contributing factors to non- utilization of IPTp-SP (observed in 3.8% of participants in this study) were unbooked status and allergy to Sulphonamides.

In contrast to compliance to IPTp-SP, this study showed that only one in five pregnant women (20%) slept under insecticide treated nets (ITNs). In portharcourt, a similar prevalence (22.4%) [9] was recorded while a study done in Sudan [16] showed only 8.9% slept under nets. In Abeokuta [18] and Bayelsa [17], 59.7% and 50.2% of study participants used bed nets. The low compliance observed in this study could be attributed to a number of factors; Firstly, majority of the participants (94.8%) had window and door nets which they could have deemed sufficient for vector control hence, they did not think it necessary to use ITNs. Also, the ITNs were not as readily available as they used to be when there were government sponsored programs distributing them for free to pregnant women and where available, the heat and discomfort encountered under the nets and the cumbersome arrangements required to put them up could be a deterrent to use. Better Compliance to use of ITNs could be achieved by increasing patient education on the importance of use of ITNs in preventing malaria in pregnancy and these nets should be made available to the pregnant women at booking.

The relationship between placental malaria parasitaemia (PMP) and low parity was statistically significant in this study (P-0.0001). Of all the women with low parity (nulliparous and primiparous), 17.1% had placental malaria parasitaemia (PMP) while only 3.3% of all the multiparous women had PMP. This is similar to the findings in a Ghana study [19] which showed that Primigravidae and secundigravidae are most at risk of developing placental malaria. Other studies have also shown that parity influences susceptibility to placental malaria. [20-25] This could be explained by the fact that pregnancy-Specific immunity against PMP is not present in the first pregnancies but develops over subsequent pregnancies.[20].

Placental malaria parasitaemia has been linked to adverse pregnancy outcomes. [5,9,16,20,26-29] In this study, PMP was significantly associated with low birth weight (P-0.0001), which is similar

to previous studies in Uyo,[5] Ile-Ilfe,[26] and Sudan.[16] It was also observed in this study that there was a significant decrease in mean birthweight in those who had PMP (2596.0 ± 352.3 g) compared to those who did not (3265.6 ± 287 g). Low birth weight (LBW) in relation to PMP could occur as a result of Intra-uterine growth restriction (IUGR) or prematurity [3]. The relationship between preterm delivery and PMP in this study was however not statistically significant (P = 0.005). This indicates a likelihood that the low birth weights observed was as a result of Intra-uterine growth restriction.

In this study, PMP was significantly associated with Cord blood parasitaemia (congenital malaria) with a relative risk of 19.8. This significant association was also found in studies done in Uyo.[5] and Maiduguri.[30] In contrast to this, a study in Colombia[31] found no malaria parasites in cord blood samples. This might be as a result of the higher prevalence of *plasmodium vivax* in Colombia which in theory fails to sequester in the placenta.[31]

The findings in this study showed that placental malaria parasitemia did not have a statistically significant association with maternal anemia (P=0.904), neither was there a statistically significant relationship between PMP and fetal anemia (P= 0.669). This was in contrast to findings in other studies, in Burkina Fasso [32] and Sudan [16] that showed a significant association between placental parasitemia and maternal anemia. It also contrasted to the findings in Benin [3] and Ghana [34] which showed an association between placental parasitemia and neonatal anemia. The differences in participant selection and inclusion criteria could account for the differences observed. This study excluded women with sickle cell anemia and Human Immunodeficiency virus infection (HIV) which are causes of anemia in our environment and these were not excluded from some of the aforementioned studies. Also, a very high percentage (97.1%) of the study participants were booked parturients in the study hospitals and received antenatal care that included daily use of hematinics, management of the risk factors for anemia and correction of anemia when detected.

Malaria in pregnancy remains a public health problem in Nigeria. The prevalence of 14.3%, 18.1% and 20.5% obtained for peripheral, cord and placental malaria parasitemia in this study reveals that more needs to be done in the prevention of malaria in pregnant women and the adverse outcomes associated with it. Low birth weight and congenital malaria is significantly associated with placental malaria parasitemia as shown in this study. Hence, all pregnant women should be properly educated on the importance of attending antenatal care, the use of insecticide treated nets and chemoprophylaxis and prompt treatment of malaria in pregnancy.

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