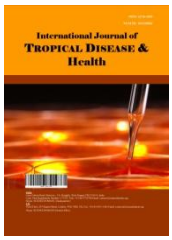

International Journal of TROPICAL DISEASE & Health

Volume 44, Issue 8, Page 13-22, 2023; Article no.IJTDH.98682
ISSN: 2278–1005, NLM ID: 101632866

Placenta and Cord Blood Malaria in Mothers and Neonates Attending Federal University Teaching Hospital, Owerri, Imo State South East Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJTDH/2023/v44i81422

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/98682

Original Research Article

Received: 22/02/2023
Accepted: 24/04/2023
Published: 02/05/2023

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ABSTRACT

Introduction: In Malaria endemic countries, gestational and cord blood malaria prevalence are highly variable. A comprehensive study to determine the prevalence of placental and cord malaria has not been undertaken in Imo state, south eastern Nigeria. Thus, the need to determine prevalence of placenta and chord blood with *Plasmodium falciparum* infection among pregnant mothers and their neonates in Federal university teaching hospital Owerri, Imo State, Nigeria.
Methodology: A hospital based cross sectional study was carried out between the months of July 2021 and June, 2022 in some public and private hospitals in Owerri, south eastern Nigeria. Malaria transmission is stable with a high seasonal transmission from July to October. Placental and umbilical cord blood was collected into an EDTA bottle from mothers who consented and their neonates respectively at delivery. The presence of *Plasmodium specie*was assessed microscopically and quantified by WHO Certified Malaria Microscopists. Parasite density was determined using WHO malaria microscopy protocol. Malaria parasite density was grouped as 1-500parasites/µl, 501-5,000parasites/µl (low), 5,001–10,000 parasites/µl (high), and >10,000 parasites/µl (very high) respectively for ease of analysis. Data was analyzed considering the parasite density grouping and parity while placenta and cord malaria prevalence were determined.
Results: Placental and congenital malaria prevalence by microscopy was 21.3% vs. 8.2%. The primigravid had the highest infection rate of 33.0%. Considering the relationship between infection prevalence and parity of pregnancy, there was a significant difference P=.001. 4.2% of 119 neonate and 13.6% of 88 neonates from multigravid and primigravid mothers respectively examined had cord malaria. There was significant difference P=.002 comparing cord malaria infection prevalence and parity of pregnancy of matched mothers. The relationship between parasite malaria density and parity of pregnancy both in placental and cord malaria were not significant. Age group 20-25 years (45%) had the highest Prevalence while age groups 26-30 years recorded a prevalence of 33.3% for the primigravid and multigravid groups, respectively (P<0.05). The Geo mean range of 220 (3-8,250) vs. 23(2-6,412) parasite/µl of blood were recorded in primipare vrs multipare group. The result of this study showed moderate placental malaria infection and a low prevalence of cord malaria by microscopy. The presence of malaria parasites in cord blood at delivery and non in maternal placental blood was also demonstrated. There is a significant association between ITN (Insecticide-Treated Net) usage compliance rate and gravidity (primigravid vs. multigravid) among pregnant mothers. There is also a statistically significant relationship between age and gravidity in the occurrence of placenta malaria, as indicated by the chi-square test results.
Conclusion: Antenatal exposure to malaria parasites may have profound effects on the fetus therefore prevention of malaria infection during pregnancy which may reduce the incidence of adverse perinatal outcomes should be strongly advocated.

Keywords: Plasmodium falciparum; placenta; umbilical cord blood; parity; malaria parasite density.

1. INTRODUCTION

“The prevalence of gestational malaria is highly variable in sub-Saharan Africa regions. Reports of prevalence ranging from 5% in Ghana [1] 19% in Malawi [2], Uganda [3], 7.53% by PCR and 18.1% respectively Burkina Faso [4,5], and in Nigeria 68.3% [6],and 65.6% [7] have been documented”. “Early peripheral infection during pregnancy may be a particularly important risk factor for placental infection, due to low immune protection at the beginning of pregnancy. Nevertheless, susceptibility may be correlated to high exposure to malaria, and repeated episodes of parasitemia, as well as the interplay between several other factors. Pregnant women are more susceptible to malaria infection than their non-pregnant counterparts in malaria endemic areas” [8,9]. "Susceptibility diminishes with successive pregnancies, and this pattern is most prominent in high transmission areas where primigravidas are significantly more susceptible to *Plasmodium falciparum* infection and disease than multigravidas” [8,9,10]. “This parity-dependent epidemiological signature distinguishes *P. falciparum* from several other infectious agents that can afflict pregnant women. Although in low transmission areas, women of all parties have increased susceptibility to malaria, infection rates may still be highest in primigravida” [11-14].

“Consequent to various evidence of the relative failure of different antimalarial drugs, particularly chloroquine, the WHO has put forward new

guidelines for combating and preventing malaria during pregnancy" [10,15]. "WHO recommends that the medicines used for IPTp be different from those used as first-line malaria treatment. SP has been widely used for chemo-prevention during pregnancy and has been shown to be efficacious, safe, well tolerated, available and inexpensive. A drug regimen that can be administered as a directly observed single dose, such as SP, is preferable to a multi-day regimen. The guidelines previously recommend that women living in high transmission areas of Africa receive intermittent preventive treatment (IPT) with an effective antimalarial agent such as sulfadoxine-pyrimethamine (SP) at scheduled antenatal visits, and all pregnant women in targeted areas should undergo at least two sessions of IPT after first fetal movements (i.e., between 20 to 35 weeks)" [15]. "However, WHO in 2022 reaffirmed that IPTp-SP should not be given before week 13 of pregnancy due to an increased risk of fetal malformation. IPT p-SP should start in the second trimester but modified the dosing intervals that doses should be given at each scheduled ANC contact until the time of delivery, provided that doses are at least one month apart. At least three doses of IPT p-SP should be received during pregnancy. WHO also reaffirmed its strong recommendation for the use of IPTp-SP in areas of moderate to high *P. falciparum* malaria transmission. The recommendation does not limit the delivery of IPT-SP to antenatal care (ANC) settings; where inequities in access to ANC services exist, other delivery methods, such as the use of community health workers, may be explored. IPT-SP is now recommended for all pregnant women, regardless of the number of pregnancies; previously, it was recommended only during a woman's first and second pregnancies. Where inequities in access to ANC services exist, other delivery methods, such as the use of community health workers, may be explored. IPT-SP is now recommended for all pregnant women, regardless of the number of pregnancies; previously, it was recommended only during a woman's first and second pregnancies" [15].

"Gestational malaria is responsible for high maternal and infantile morbidity; a high susceptibility to malaria infection during the first months of life is one of the serious consequences of Malaria vertical transmission on the newborn [16] and also an early susceptibility to other infections" [17]. "This susceptibility to infection is due to neonatal T cells imbalance and pro inflammatory and anti-inflammatory immune responses after their sensitization by *Plasmodium falciparum in utero"* [18-20] "Exposure of a fetus to malaria may prime immune responses or induce immune tolerance that may subsequently affect susceptibility to infection and disease during infancy" [21].

In this present study, we compared prevalence of malaria in placenta as compared to chord blood We went ahead to also quantify malaria parasites in paired maternal placental-blood, and cord-blood samples obtained from women and their neonates living in a malaria-endemic area of Nigeria. The identification and quantitation of malaria parasite was done using light microscopy method, which is more sensitive and specific when performed by a competent/expert microscopist.

2. MATERIALS AND METHODS

2.1 Enrolment of Study Participants

The study was conducted in Imo state, Nigeria, specifically at the Federal university teaching hospital, Owerri, a government tertiary health facility. Two hundred and seven (207) pregnant women who attended their antenatal clinics (ANCs) in the hospital (booked) who gave written consent to participate in the study were recruited. These women completed a questionnaire to determine their demographic and maternal characteristics (age, gravidity, gestational age, number of antenatal visits, SP dosage, and history of fever attack during pregnancy). Some of the Exclusion criteria were (a) Expectant mothers with evidence of chronic illness and complicated pregnancy (hypertension, preeclampsia, diabetes) (b) multiple pregnancies. Those in excluded were considered to be high risk group. Codes were given to the study participants and their newborn immediately after delivery and all forms personal identifiers removed to ensure confidentiality.

2.2 Collection of Samples

Blood samples were collected from cords of live, singleton, full term neonates delivered in the hospital and also from their matched mother's placenta. Multiple aspirations were made on the maternal half of the placenta, just below halfway between the maternal and fetal surfaces using a 19-gauge needle attached to a 2ml syringe. From the aspirates (blood), duplicate thick and thin films were made on clean microscopic slides. Cord blood was collected by cannulation of the umbilical vein after inversion of the placenta and cleaning of the umbilical cord with 70% alcohol to avoid

maternal blood contamination and incised at ~15cm from its attachment to the placenta with a fresh blade.

2.3 Laboratory Methods

Thin and thick smears were prepared for each participant following standard procedures for malaria microscopy. Examination of 3% Geimsa stained blood film was done using x100 objective. Two competent microscopists read each slide, and when there was discordance in reading, a third microscopist reread the slide and served as a tie breaker. Essentially, the discordance level for the acceptance of any two parasite counts was set at less than 20%.

2.4 Data Analysis

The data generated from the study were analyzed using EPIINFO 2002 statistical software (CDC, Atlanta, GA, USA).Tests for associations and differences were done by chi-square analysis and Fischer Exact test, analysis of variance was done as appropriate. A value less than 0.05 was taken as significant.

3. RESULTS

Table 1 provides the profile of the study participants, while Table 2 displays the overall prevalence of placental and umbilical cord malaria. The results from Table 1 indicate that the study found a placental infection prevalence of 21.3%. Primipara (first-time mothers) had the highest infection rate at 33.0%, and there was a significant difference (P=.001) in infection prevalence based on parity of pregnancy.

The overall cord malaria infection rate was 8.2%, with 4.2% of neonates from multipara mothers and 13.6% of neonates from primipara mothers showing cord malaria. There was a significant difference (P=0.02) in cord malaria infection prevalence based on parity of pregnancy among matched mothers.

Table 1. Profile of study participants

Character	Frequency (%)
Number of participants	**207**
Age (years)	
Mean ±SD	23.3±18.4
20-25	43 (20.8%)
26-30	63 (30.4%)
31-35	62 (30.0%)
36-40	26 (12.6%)
41-45	13 (6.3%)
Microscopy(placenta)	
Positive	44 (21.3%)
Negative	163(78.7%)
Primigravida	29 (33.0%)
multigravida	15 (12.6%)
Microscopy(cord)	
Positive	17 (8.2%)
Negative	190 (98.1%)
Primigravida (neonate)	12 (13.6%)
Multigravida (neonate)	05 (4.2%)
Placental Parasitemia Geomean (range)	
Primigravida	220(3-8,250) (p/µL)
Multigravida	23(2-6,412) (p/µL)
1-500	14 (31.8%)
501-5,000	25 (56.8%)
5001-10,000	5 (11.3%)
>10,000	0 (00%)

Table 2. Overall prevalence of placental and umbilical cord malaria

Parity	No Examined	No infected		No uninfected	
		Placenta	Cord	Placenta	Cord
Primipara	88	29(33.0)	12(13.6)	59(67.1)	76(86.4)
Multipara	119	15(12.6)	5(4.2)	104(87.4)	114(95.8)
Total	207	44(21.3)	17(8.2)	163(78.7)	190(91.8)

Table 3. Relationship between parity of pregnancy and placental /cord parasite malaria density

Density (p/µL)	Primipara Freq. (%)		Multipara Freq. (%)	
	Placenta	Cord	Placenta	Cord
1-500 (low)	9(31.0)	8(66.7)	5(33.3)	3(60.0)
501-5000 (mid)	17(58.6)	4(33.3)	8(53.3)	2(40.0)
5001-10,000 (high)	3(10.3)	0 (0.0)	2(13.3)	0 (0.0)
>10,000 (very high)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Our calculated chi-square values of 11.12 for infected placentas and 2.14 for infected cords are greater than the critical value of 3.84. Therefore, we reject the null hypothesis and conclude that there is a statistically significant association between parity of pregnancy and placental/cord parasite malaria density. Specifically, primipara women are more likely to have infected placentas and cords compared to multipara women. These findings suggest that parity of pregnancy may be an important factor in the risk of placental/cord parasite malaria density, with primipara women being at higher risk compared to multipara women.

The odds ratio (OR) of having placental/cord malaria with "5001-10,000 (high)" parasite density in primipara compared to multipara is 1.67 (95% CI: 0.54 to 5.16). This suggests that primipara may have higher odds of having placental/cord malaria with high parasite density compared to multipara, although the association is not statistically significant as the confidence interval includes 1.0. Further research with larger sample sizes may be needed to confirm these findings.

The chi-square test revealed a statistically significant association between age and gravidity in the distribution of placenta malaria (χ^2 = 23.70, df = 4, p < 0.05). The odds ratio (OR) for having placenta malaria in primigravid women compared to multigravid women was 2.52 (95% CI: 1.29, 4.93). This means that there is a statistically significant relationship between age and gravidity in the occurrence of placenta malaria, as indicated by the chi-square test results. Specifically, primigravid women have higher odds of experiencing placenta malaria compared to multigravid women, with an odds ratio of 2.52 (95% confidence interval:1.29 to 4.93).This suggests that being a primigravid woman may be a risk factor for placenta malaria compared to being a multigravid woman.

The chi-square test result with a calculated X^2 = 0.2666 ($p<0.05$) suggests that there is no significant association between academic status and placental malaria infection among pregnant women. This is supported by the calculated odds ratio (OR) value of 0.2697 [95%: 0.2543 - 0.7672.], which indicates that the odds of placental malaria infection among uninfected women are not significantly different from the odds of placental malaria infection among infected women, based on academic status.

The results of the chi-square test and odds ratio analysis suggest that there is a significant association between ITN (Insecticide-Treated Net) usage compliance rate and gravidity (primigravid vs. multigravid) among pregnant mothers. The chi-square test, with a calculated chi-square statistic of 6.08 (greater than the critical chi-square value of 5.99 at α = 0.05), indicates that there is a statistically significant difference in ITN usage compliance rate between primigravid and multigravid mothers. This suggests that gravidity status may be a significant factor influencing ITN usage among pregnant mothers.

The odds ratio (OR) of 1.87 indicates that primigravid mothers have 1.87 times higher odds of complying with ITN usage compared to multigravid mothers. This suggests that being a primigravid mother may be associated with a higher likelihood of ITN usage compliance.

The 95% confidence interval (CI) for the odds ratio, ranging from 1.013 to 3.434, indicates that the true population odds ratio is likely to fall between these values with 95% confidence. This further supports the finding that there is a significant association between ITN usage compliance rate and gravidity among pregnant mothers.

Table 4. Age related distribution of placenta malaria

Age (years)	Primigravid		Multigravid	
	No examined	No. infected	No examined	No. infected
20-25	20	9(45.0)	23	2(13.3)
26-30	29	10(34.5)	34	5(33.3)
31-35	22	7 (31.8)	40	4 (26.7)
36-40	11	2 (18.1)	15	3(20.0)
41-45	6	1(16.7)	7	1(6.7)
Total	88	29(33.0)	119	15(12.6)

Table 5. Academic status/ rate of placental malaria infection

Academic status	Total	Uninfected	Infected
Non formal Education	15	11(73.5)	4(26.7)
Primary education	62	50(80.6)	12(19.4)
Secondary education	89	70(78.7)	19(21.3)
Tertiary education	41	32(78.0)	9(22.0)
Total	207	163(78.7)	44(21.3)

Table 6. ITN Usage compliance rate among pregnant mothers

ITN USAGE	Total	Primigravid	Multigavid
Daily	33(15.9)	18(20.4)	15(12.6)
Once a week	58(28.0)	22(25.0)	36(30.3)
Not at all	122(58.9)	48(54.5)	68(57.1)
Total	207	88	119

Key: ITN: Insecticide Treated Nets

Table 7. Antimalaria drug usage by pregnant mothers

SP/anti malaria intake	No Examined	%Primigravid	%Multigravid
(2-4 times in 9months	81(39.1)	42(47.7)	39(32.7)
Once in 9 months	94(45.4)	35(39.8)	59(49.6)
None	32 (15.5)	11(12.5)	21(17.6)
Total	207	88	119

Table 7 shows the association between antimalaria drug usage and gravidity (primigravid vs. multigravid) among pregnant mothers. The calculated chi-square value was 9.87 with 2 degrees of freedom, and p=<0.001. This indicates that there is a significant association between antimalaria drug usage and gravidity among pregnant mothers, suggesting that gravidity may be a factor influencing antimalaria drug usage. The calculated Odds Ratio (OR) for antimalaria drug usage between Primigravid and Multigravid pregnant mothers was approximately 1.874.This indicates that Primigravid pregnant mothers have 1.874 times higher odds of using antimalaria drugs compared to Multigravid pregnant mothers [95% C.I. 1.3902 - 3.276].

4. DISCUSSION

This study showed placental and cord malaria with prevalence rate of 21.3% and 8.2% respectively. Similar studies conducted in parts of south-eastern Nigeria on placental malaria showed higher prevalence of 69.6% and 70.5% which they attributed majorly to un-booked maternal status, nonuse of both IPT and insecticide treated nets (ITN) [5,6].

This study is in consonance with Previous Studies that have demonstrated the relationship between placental malaria and parity and have reported the prevalence to be higher in primigravidas than multigravidas, and in these studies, results are controlled for age [22-25].

“The exact reason why primigravidas are more susceptible to placental malaria and suffer from its consequences more than multigravidas is still of great concern and research interest. This notwithstanding, is an attempt to understand the reason for the primigravidae susceptibility. One study explained that pregnancy is associated with a decrease in immunity, which is more pronounced in primigravidae than in multigravidas and may be associated with age” [26] “Immunological studies have shown that this increase in susceptibility could be related to the property of parasitized erythrocytes to adhere to chondroitin sulfate A (CSA) expressed by the syncytiotrophoblast of the placenta” [27,28,29]. “Thus, the placenta may select for the CSA-binding *P. falciparum* phenotype, putting primigravidae with no previous exposure to this parasite form at increased risk for developing placental malaria. The decreasing susceptibility to pregnancy-associated malaria with increasing parity is reflected in the acquisition of antibodies specific to parasites’ variant antigens expressed on the surface of infected erythrocytes” [30]. Another possible explanation for this parity-

related susceptibility is given by the findings of Duffy and Fried [31], who showed that "multigravida mothers develop malaria antibodies that block adhesion of parasites to CSA receptors in the placentae in subsequent pregnancies".

The Geo mean of placental parasite density in this study was 851 (6-9830) parasite/µl, while the primigravidae recorded a Geo mean of 420(20-8,942) parasite/µl, multigravidas had a Geo mean of 431(6- 6,200) parasite/µl. It is also important to note that both the primigravidae and multigravidas recorded almost same frequency of distribution parasite density. This study is therefore in contrast with [32] who reported that the primigravidae had a higher mean parasite density (2,155/micro l) when compared with the multigravidas (1,950/micro l). Parity in this study had no effect on placental malaria parasite density however there was significant difference in cord-blood parasitemia obtained from newborns of women with placental malaria, compared with parasitemia of cord-blood samples obtained from newborns of women without placental malaria.

In this study, the daily use of malaria preventive measure such as ITNs was low (15 .9%) while 58.9% of pregnant mothers never slept under an LLINs during their gestational period . it was observed also that only 39% of the women had SP administration for IPTp by WHO recommendation [15] and this suggest a low compliance rate.

Furthermore, considering placental malaria prevalence by age in this study; 20-25 years having the highest prevalence in the primigravidae, which agrees with a report that suggested the role age-associated immunity may play in limiting *P. falciparum* to low parasite densities in areas of high and stable transmission [10]. The low Geo mean parasite density may be explained by some favorable characteristics of the study site/ population but the reason for the shift of placental malaria prevalence in multigravidas from the widely canvassed <20 years to 26-30 years is yet to be understood. It may be attributed but not limited to low complaint to intake of administered SP for IPTp among the group, further investigations are advocated for especially as regards to hormonal and immunologic response [10].

Limitations encountered in this study were seen during the determination of placental and cord malaria primarily by blood-smear microscopy and not by the use of placental biopsy for PM or RTQ-PCR which is more sensitive. Some studies that are in concomitant with the present findings that suggest that with the limitation encountered above, it could account for the low parasitemia. Other methods other than microscopy i.e. polymerase chain reaction (PCR) assays has been seen to be sensitive and further has identified falciparum malaria parasites in 10%–32% of cord-blood samples obtained from individuals in areas where malaria is endemic [11-14].This has therefore suggested that the presence of malaria parasites in cord blood occurs with greater frequency than previously appreciated.

5. CONCLUSION

There is sparse evidence on placenta malaria using biopsy specimen in South eastern Nigeria and this has permitted the determination of only acute placental malaria and not determination of either the severity of placental malaria or whether changes had occurred. Malaria still remains a public health problem among pregnant women and neonates. This study has raised concern on possible burden of cord malaria on neonates and therefore advocates for further studies on the use of more sensitive and specific approach to determine the prevalence and severity of placental/ cord malaria as well as the possible outcomes of the frequency of administration of IPTP during pregnancy.

CONSENT AND ETHICAL APPROVAL

Written consent was obtained from patients before carrying out the study. Approvals to conduct this study were obtained from the Ethical committee of Federal university teaching hospital Owerri, Imo state and the protocol was conducted in accordance with Good clinical practice (GCP), Good Clinical Laboratory Practices (GCLP).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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