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# Risk factors for placental malaria and associated low birth weight in a rural high malaria transmission setting of Cote d'Ivoire

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## Abstract

**Background:** Placental malaria (PM) is associated with increased risk of both maternal and neonatal adverse outcomes. The objective of this study was to assess risks factors associated with PM including intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP).

**Methods:** A cross-sectional study was conducted at Ayame hospital in the southern region of Cote d'Ivoire between August 2016 and March 2017. Sociodemographic baseline characteristic and antenatal data were obtained from the mother's antenatal card and included timing and number of IPTp-SP doses. Newborn characteristics were recorded.

Peripheral blood as well as placental and cord blood were used to prepare thick and thin blood films. In addition, pieces of placental tissues were used to prepare impression smears. Regression logistics were used to study factors associated with PM and low birth weight (LBW) (<2.500 g).

**Results:** Three hundred delivered women were enrolled in the study. The mean age of the participants was  $25 \pm 6.5$  years and most participants were multigravida (52.8%). The coverage rate of IPTp-SP with the full three doses recommended was 27.8%. Overall, 7.3% (22/300) of women examined had PM detected by microscopy using impression smear (22/300). Multivariate analysis showed that significant risks factors of PM were maternal peripheral parasitemia at delivery ( $P < 0.0001$ ), residence ( $P = 0.03$ ), and not sleeping under long-lasting insecticide treated nets (LLINs) ( $P = 0.006$ ). LBW infants were born to 22.7% (5/22) of women with PM and 13.3% (37/278) of women without PM ( $P = 0.47$ ). Only primiparous was associated with LBW in the multivariable analysis ( $P = 0.04$ ).

**Conclusion:** The prevalence of PM was 7.3%. Low parity, residence and not using LLINs and maternal peripheral parasitemia were identified as risks factors. PM was associated with LBW. Implementation of IPTp-SP should be improved by the National Malaria Control Program in rural settings.

**Keywords:** Ayame Cote d'Ivoire, low birth weight, placental malaria, risks factors

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## INTRODUCTION

Malaria in pregnancy (MIP) is of major public health concern. In Sub-Saharan Africa, 32 million pregnant women are at risk of acquiring malaria during pregnancy every year.<sup>[1,2]</sup>

In high transmission settings, pregnant women are particularly susceptible to malaria infection and this susceptibility is attributed to immunological changes occurring in pregnancy.

In such settings, MIP is mainly characterized by asymptomatic parasitemia often with sequestration of parasites in the placenta leading to local inflammation and may result in placental infection in the absence of detectable peripheral blood infection.<sup>[3]</sup>

Placental malaria (PM) is therefore a major manifestation of MIP. PM is associated with increased risk of both maternal and neonatal adverse outcomes including maternal anaemia (which leads to increased maternal mortality), delivery of low birth weight (LBW) infants, premature delivery, stillbirth, and increased perinatal and infant mortality.<sup>[2,4]</sup> Previous studies estimating the burden of PM in sub-Saharan Africa have yielded variable findings.<sup>[5]</sup>

To prevent malaria during pregnancy and its adverse outcomes, the World Health Organization (WHO) recommends the use of intermittent preventive treatment with sulfadoxine-pyrimethamine (IPTp-SP), sleeping under an insecticide treated bed net (ITN), and prompt management of malaria cases and anaemia.<sup>[6]</sup>

IPTp consists of administering, to all pregnant women, at least two doses of SP during the second and third trimesters of pregnancy during routinely scheduled antenatal clinic visits irrespective of the presence of signs for a malaria infection.<sup>[6-8]</sup>

The use of IPTp-SP has been shown to increase birth weight and reduce the incidence of LBW as well as pregnancy-related parasitemia and anaemia.<sup>[9-12]</sup>

In Cote d'Ivoire, the National Malaria Control Program implemented IPTp strategy since 2005 with two doses of SP. In 2013, the country has revised this strategy and adopted a policy of providing three or more doses of SP to pregnant women as recommended by the WHO.<sup>[1]</sup>

Few data on PM and IPTp-SP are available in Cote d'Ivoire particularly in rural setting.<sup>[13,14]</sup>

The main objective of this study was to determine the risk factors of PM, including SP prophylaxis as IPTp during pregnancy and associated LBW in a rural setting of Cote d'Ivoire.

## METHODS

### Study design and site

We conducted a cross-sectional study from August 2016 to March 2017 in Ayame hospital in southern region of Cote d'Ivoire. In the study area, malaria transmission is intense and perennial, with recrudescence during the rainy season.

The main malaria vectors are *Anopheles gambiae* and *Anopheles funestus*. *Plasmodium falciparum* is the predominant plasmodial species. Malaria control strategies are mainly based on the WHO long-lasting insecticide treated nets (LLINs), prompt diagnosis and effective treatment, and IPTp-SP.

### Study population

The study population was all postpartum women aged 15–49 years who had just delivered (<24 h) and those who delivered at home but visited the health facilities for check-up.

HIV-positive women receiving antiretroviral treatment or prophylactic treatment with co-trimoxazole were excluded from the study, since IPTp-SP is not recommended in these women due to the potential adverse drug reactions. Written informed consents were obtained from all women before enrolment into the study.

### Study procedures

Consenting women who met the study inclusion criteria were enrolled at the time of delivery.

A structured questionnaire survey was conducted to document sociodemographic data including age, residence, marital status, education, and occupation, the use of LLINs and obstetric history. Antenatal data were obtained from the mother's antenatal card. These data included parity, gestational age at the first antenatal care (ANC), number of ANC, and timing and number of IPTp-SP doses as well as previous malaria episode and treatment received.

Immediately after delivery, babies were weighed using a hanging weighing scale (Model 180; Salter Brecknell, West Midlands, United Kingdom). Data regarding newborn characteristics (vital status at birth, birth weight, sex, and the presence of twins or malformation) were collected. Blood smears were made with blood collected from mother's peripheral venous, from the maternal side of the delivered placenta, and from the umbilical vein cord. Placental tissue

samples were also collected from the maternal side of the placenta with approximately 2 cm × 2 cm in length and width, and 1 cm in depth and were used to prepare impression smears after swabbing it on blotting paper.

All blood smears were stained with 5% Giemsa for 25 min and examined for malaria parasites by standard microscopy. Two hundred high-power fields were examined before the smear was considered negative.

Parasite density was determined as previously described (Shute *et al.*, 1988). The parasite density (per 1  $\mu$ L of blood) was calculated, assuming a normal leukocyte level of 8000/ $\mu$ L.

To determine the percentage of malaria parasitemia from placental impression smears, malaria parasite-infected red cells were counted against 2000 erythrocytes.

Placental infection status was categorized as infected (the presence of any asexual parasite stages in the placenta and or malaria pigment) and noninfected (no parasites or pigment).

The slides were then viewed under a microscope using oil immersion at  $\times$  100 magnification by two independent microscopists.

In cases of discrepancy, a third microscopist counted the number of parasites in the films. The average of two counts that agreed was used as the final level of parasitemia.

### Sample size

Using a prevalence rate of placental parasitemia from previous studies,<sup>[13,14]</sup> a minimum sample size of 200 women was estimated to provide a power of 80% with 5% precision. A total of 300 pregnant women with study's inclusion criteria were consecutively recruited which increased both the power and precision.

### Statistical analysis

Differences in frequencies were compared by either Chi-squared or Fisher's exact tests as appropriate, and continuous variables by Student's *t*-test when the data were normally distributed. Nonparametric tests were used for nonnormally distributed data. In the multivariable analysis, the factors associated with the dependent variable (LBW or PM) based on univariate analysis were included. Statistical analysis was performed using Stata<sup>®</sup> version 10.0 (StataCorp LP, College Station, TX, USA).

### Ethical issues

Prior to enrolment, participants were informed on the objectives, procedures, and benefits of the study. Written

consent was obtained before the participants were enrolled into the study. Approval for this study was obtained from the Comité National d'Ethique des Sciences de la Vie et de la Sante of Cote d'Ivoire.

## RESULTS

### Sociodemographic characteristics of participants

A total of 300 delivered women were enrolled. Characteristics of the study population are summarized in Table 1. The mean age of the participants was 25 years. Most participants were multigravida (52.8%). Most of the participants have no education (71.8%). The median number of ANC visits was 3 (ranged from 0 to 5) and over 38.6% of mothers attended at least four ANC visits. A total of 18 participants (6.1%) did not receive any dose of IPTp-SP during pregnancy, while 39% and 27.8% of participants received 2 and 3 doses, respectively.

Pregnant women in the age group of 20–24 years had the highest uptake of optimal SP doses compared to the rest of the women. This was also observed with multigravida participants (%) ( $P = 0.04$ ). Antenatal clinic attendance (scheduled visits) was significantly higher with at least three ANC (62.6%). Participants were aware of the use of ITN (221; 75%) as methods of malaria prevention in pregnancy.

### Placental malaria

Overall, 7.3% ( $n = 22/300$ ) of women examined had PM detected by microscopy using impression smear (22/300).

The prevalence of PM was recorded with 13.16% (10/76), 9.38% (6/64), and 3.75% (6/160), respectively, in primigravidae, secondigravidae, and multigravidae women. The prevalence of women with peripheral parasitemia was only 1.3% (4/300).

Risks factors of PM in univariate analysis were maternal peripheral parasitemia at delivery primigravide (odds ratio [OR] = 3.88, 95% confidence interval [CI] = 1.38–11.84;  $P = 0.01$ ), (OR = 17, 95% CI = 4.83–60.44;  $P < 0.0001$ ), neighboring villages (OR = 4.46, 95% CI = 1.47–19.33;  $P = 0.01$ ), and the none use of LLINs (OR = 2.62, 95% CI = 1.06–6.35;  $P = 0.03$ ).

Multivariate analysis showed that significant risks factors of PM were maternal peripheral parasitemia at delivery (OR = 22.8, 95% CI = 5.15–111.0;  $P < 0.0001$ ), locality (OR = 4.1, 95% CI = 1.24–18.84,  $P = 0.03$ ), and the lack of usage of LLINs (OR = 4.5, 95% CI = 1.55–14.22,  $P = 0.006$ ) [Table 2].

**Table 1: Sociodemographic characteristics in delivered women according to the number intermittent preventive treatment with sulfadoxine-pyrimethamine doses (n=295)**

	IPTp-SP dose					P
	Total (n=295)	0 (n=18)	1 (n=80)	2 (n=115)	≥3 (n=82)	
Age (year)						
Median±SD	25±6.5	28±6.4	25±7.1	24±5.8	25±6.8	0.13
<20	43 (14.5)	3 (16.6)	10 (12.5)	17 (14.7)	13 (15.8)	0.92
20-24	90 (30.5)	2 (11.1)	21 (26.2)	41 (35.6)	26 (31.7)	0.14
25-29	72 (24.4)	5 (27.7)	19 (23.7)	29 (25.2)	19 (23.1)	0.97
≥30	90 (30.5)	8 (44.4)	30 (37.5)	28 (24.3)	24 (29.2)	0.13
Gravidy						
Median±SD	3±2.1	4±2.5	3±2.3	2±1.9	2.5±2.0	0.003
1	76 (25.7)	3 (16.6)	13 (16.2)	35 (30.4)	25 (30.4)	0.07
2	63 (21.3)	3 (16.6)	16 (20.0)	28 (24.3)	16 (19.5)	0.77
≥3	156 (52.8)	12 (66.6)	51 (63.7)	52 (45.2)	41 (50)	0.04
Number of ANC visit						
Median±SD	3±1.5	1±1.8	2±1.1	3±1.0	4.5±1.0	<0.0001
0	3 (1.0)	3 (16.6)	0 (00)	0 (00)	0 (00)	0.0001
1	47 (15.9)	10 (55.5)	37 (46.2)	0 (00)	0 (00)	<0.0001
2	60 (20.3)	3 (16.6)	25 (31.2)	32 (27.8)	0 (00)	<0.0001
3	71 (24.0)	1 (5.5)	11 (13.7)	44 (38.2)	15 (18.3)	<0.0001
≥4	114 (38.6)	1 (5.56)	7 (8.7)	39 (33.9)	67 (81.7)	<0.0001
Birth weight (g)						
Median±SD	3000±548	3000±500	3100±500	2900±600	3000±400	0.20
<2500	42 (14.2)	2 (11.1)	10 (12.5)	21 (18.2)	9 (10.9)	0.50
≥2500	253 (85.8)	16 (88.9)	70 (87.5)	94 (81.8)	73 (89.0)	0.46
Locality						
Ayame city	116 (39.3)	5 (27.7)	27 (33.7)	44 (38.2)	40 (48.8)	0.15
Neighbors villages	170 (57.6)	11 (61.1)	52 (65.0)	66 (57.4)	41 (50.0)	0.28
Yaou	7 (2.3)	2 (11.1)	1 (1.2)	3 (2.6)	1 (1.2)	0.13
Others	2 (0.6)	0 (00)	0 (00)	2 (1.6)	0 (00)	1
Use of LLINs						
No	74 (25.0)	9 (50)	29 (36.2)	26 (22.6)	10 (12.2)	0.0002
Yes	221 (75.0)	9 (50)	51 (63.8)	89 (77.4)	72 (87.8)	0.0002
Occupation						
Student	17 (5.7)	2 (11.1)	4 (5.0)	7 (6.1)	4 (4.9)	0.6
House-wife	238 (80.6)	15 (83.3)	70 (87.5)	96 (83.4)	57 (69.5)	0.02
Farmer	6 (2.0)	0 (00)	2 (2.5)	2 (1.7)	2 (2.4)	1
Public servant	34 (11.5)	1 (5.5)	4 (5.0)	10 (8.7)	19 (23.2)	0.002
Education						
None	212 (71.8)	13 (72.2)	67 (83.7)	85 (73.9)	47 (57.3)	0.002
Primary	53 (17.9)	2 (11.1)	8 (10.0)	19 (16.5)	24 (29.2)	0.01
Secondary	22 (7.4)	1 (5.5)	3 (3.7)	8 (6.9)	10 (12.2)	0.22
University	8 (2.7)	2 (11.1)	2 (2.5)	3 (2.6)	1 (1.2)	0.1

IPTp-SP: Intermittent preventive treatment with sulfadoxine-pyrimethamine, LLINs: Long lasting insecticidal nets, ANC: Antenatal clinic, SD: Standard deviation

### Low birth weight

The overall prevalence of LBW babies was 14% as shown in Table 3. LBW infants were born to 22.7% (5/22) of women with PM and 13.3% (37/278) of women without PM ( $P = 0.47$ ). Only primiparous was associated with LBW in the multivariable analysis (OR = 2.35, 95% CI = 1.02–5.52,  $P = 0.04$ ).

### DISCUSSION

PM is still a major threat to the well-being of both the mother and fetus. It is a common complication of MIP especially in areas where malaria is endemic. The study documented a prevalence of PM of 7.3% among women who delivered at Ayame's hospital. This prevalence is similar to that reported by Toure *et al.*<sup>[13]</sup>

The prevalence of PM parasitemia (7.3%) was higher than the reported prevalence (4.8%) by Vanga-Bosson *et al.*<sup>[14]</sup> Low prevalence PM has been also reported in Ghana,<sup>[15]</sup> and Zanzibar.<sup>[16]</sup>

The prevalence of PM varies in different study populations depending on the population characteristics and the diagnostic methods used. Various methods are available for the diagnosis of PM. However, histological analysis of the placenta is more sensitive and has been considered the gold standard for the diagnosis.<sup>[17,18]</sup>

It is plausible that many women may have had submicroscopic placental parasites undetected by microscopy.

Residence and maternal peripheral parasitemia were significantly associated in this study with PM. The majority

**Table 2: Factors associated with placental malaria: logistic regression model (n=300)**

Factors associated	n	Placental malaria, n (%)	Univariate analysis			Multivariate analysis		
			OR	95% CI	P	OR	95% CI	P
Age (year)								
<20	43	3 (6.98)	1	-	-	1	-	-
20-24	91	11 (12.09)	1.83	0.53-8.43	0.37	2.51	0.55-14.13	0.25
25-29	74	6 (8.11)	1.17	0.29-5.81	0.82	2.76	0.36-23.28	0.32
≥30	92	2 (2.17)	0.29	0.03-1.85	0.19	1.31	0.10-15.40	0.82
Gravidity								
1	76	10 (13.16)	3.88	1.38-11.84	0.01	4.03	0.85-24.60	0.08
2	64	6 (9.38)	2.65	0.80-8.80	0.10	1.62	0.34-7.73	0.53
≥3	160	6 (3.75)	1	-	-	1	-	-
IPTp-SP								
0	18	1 (5.56)	1	-	-	-	-	-
1	80	5 (6.25)	1.13	0.16-22.45	0.91	-	-	-
2	115	11 (9.57)	1.79	0.31-33.91	0.58	-	-	-
3	82	3 (3.66)	0.64	0.07-13.48	0.71	-	-	-
Malaria during pregnancy								
Positive	46	5 (10.87)	1.70	0.53-4.57	0.32	1.72	0.48-5.47	0.37
Negative	254	17 (6.69)	1	-	-	1	-	-
Peripheral malaria								
Positive	12	6 (50.0)	17.0	4.83-60.44	<0.0001	22.8	5.15-111.0	<0.0001
Negative	288	16 (5.56)	1	-	-	1	-	-
Locality								
Ayame	118	3 (2.54)	1	-	-	1	-	-
Neighbors villages	172	17 (9.88)	4.46	1.47-19.33	0.01	4.1	1.24-18.84	0.03
Use of LLINs								
No	77	10 (12.98)	2.62	1.06-6.35	0.03	4.55	1.55-14.22	0.006
Yes	223	12 (5.38)	1	-	-	1	-	-
Profession								
Student	17	2 (11.76)	4.80	0.42-107.9	0.21	-	-	-
House-wife/farmer	246	19 (7.72)	3.01	0.59-54.96	0.28	-	-	-
Public servant	37	1 (2.70)	1	-	-	-	-	-

IPTp-SP: Intermittent preventive treatment with sulfadoxine-pyrimethamine, LLINs: Long lasting insecticidal nets, OR: Odds ratio, CI: Confidence interval

of participants resided outside of Ayame in neighboring villages (57.3%) where the transmission of malaria is thought to be higher than in Ayame town.

This study demonstrated that primigravida are 4.08 times more likely to have PM than multigravida.

It is understood from previous studies;<sup>[19]</sup> that primigravidae are at a higher risk of PM due to the absence of previous exposure to *P. falciparum* and therefore they have not yet developed protective antibodies that block the adhesion of parasitized erythrocytes to chondroitin sulfate A in the placental intervillous space to promote clearance of parasites.

A study conducted by Ndeserua *et al.*, in Tanzania, indicated that factors associated with increased risk of PM were primigravidity and history of fever during pregnancy.<sup>[20]</sup>

The use of bed nets was associated with reduced odds of PM despite a low coverage of ITNs. Educating pregnant women on the role of ITNs in preventing malaria will impact positively in reducing the prevalence of malaria.

In this study, there was significant reduction in the prevalence of PM with the use of the full dose of IPT

with SP during pregnancy. This was in accordance with previous studies.<sup>[9-12]</sup>

We found a prevalence of LBW of 13.5%, which is much higher than the prevalence rate of 9.6% reported in a previous study which demonstrated also a strong association between PM and LBW.<sup>[13]</sup>

In the current study, the prevalence of LBW tended to be higher in babies born from mothers with PM parasitemia compared with that of babies born from uninfected mothers although such difference did not reach statistical significance. The more likely explanation is that our small sample size might have not provided enough strength to our statistics.

Elsewhere in Africa, PM was associated with LBW.<sup>[21-23]</sup> In Ethiopia, the incidence rate of LBW was 17.1% among mothers in the age group of 18–35 years,<sup>[24]</sup> while in Uganda, the prevalence of LBW was 25.5%.<sup>[24]</sup>

Besides, there are other factors that affect LBWs such as low or no education for the mother, being unmarried, and late or less frequent attendance of ANC services and place of birth.<sup>[24,25-30]</sup> Spontaneous abortion and

**Table 3: Factors associated with low birth weight: logistic regression model (n=300)**

Factors associated	n	Weight <2500 g, n (%)	Univariate analysis			Multivariate analysis		
			OR	95% CI	P	OR	95% CI	P
Parity								
Primiparous	87	20 (22.9)	2.6	1.26-5.49	0.01	2.35	1.02-5.52	0.04
secondiparous	67	7 (10.4)	1.01	0.37-2.55	0.96	1.05	0.37-2.77	0.91
Multiparous	146	15 (10.2)	1	-	-	1	-	-
IPTp-SP								
0	18	2 (11.1)	1	-	-	1	-	-
1	80	10 (12.5)	1.14	0.26-7.90	0.87	1.07	0.23-7.85	0.93
2	115	21 (18.2)	1.78	0.45-11.84	0.46	2.44	0.41-22.10	0.36
3	82	9 (10.9)	0.98	0.22-6.87	0.98	1.62	0.23-16.55	0.64
Number of ANC visit								
0	3	0	NA	NA	NA	NA	NA	NA
1	48	8 (16.6)	1	-	-	1	-	-
2	60	11 (18.3)	1.22	0.41-3.15	0.82	0.58	0.13-2.32	0.44
3	189	23 (12.1)	0.69	0.29-1.75	0.41	0.28	0.05-1.25	0.10
Placental malaria								
Positive	22	5 (22.7)	1.9	0.6-5.18	0.22	1.37	0.33-4.82	0.63
Negative	278	37 (13.3)	1	-	-	1	-	-
Malaria during pregnancy								
Positive	46	8 (17.3)	1.36	0.55-3.04	0.47	1.76	0.66-4.31	0.23
Negative	254	34 (13.3)	1	-	-	1	-	-
Peripheral malaria								
Positive	12	4 (33.3)	3.28	0.84-10.9	0.06	2.97	0.59-13.45	0.16
Negative	288	38 (13.1)	1	-	-	1	-	-
Use of LLINs								
No	77	8 (10.38)	0.64	0.26-1.39	0.29	0.62	0.23-1.64	0.29
Yes	223	34 (15.24)	1	-	-	1	-	-
Profession								
Student	17	4 (23.52)	2.53	0.53-12.26	0.23	1.41	0.25-8.02	0.69
Homemaker/farmer	246	34 (13.82)	1.32	0.48-4.64	0.61	0.93	3.57	0.91
Public servant	37	4 (10.81)	1	-	-	1	-	1

IPTp-SP: Intermittent preventive treatment with sulfadoxine-pyrimethamine, LLINs: Long lasting insecticidal nets, OR: Odds ratio, CI: Confidence interval, NA: Not available

LBW (<2500 g) are other effects attributable to PM as indirect consequences on the foetus from placental sequestration of *P. falciparum*-infected red blood cells.

Results from this study showed that only 27.8% of pregnant women took the WHO recommended three doses of SP for IPTp. Many other studies in Sub-Saharan Africa have confirmed this low utilization.<sup>[31-33]</sup> This low uptake of a full of IPTp was in contrast with the relatively high rate of ANC visit (62.6% with at least three ANC) which could give an opportunity of taking a full course of IPTp. In contrast, some studies reported high coverage of IPTp with SP.<sup>[34]</sup>

The study has several limitations. First, the prevalence of PM may be higher if histology method the gold standard method was used instead of microscopy.

Second, findings of this study are limited in terms of overall generalization and impact since the study might have been faced with recall bias. Furthermore, the study was conducted at the health facilities, and this may lead to selection bias as the situation of pregnant women who do not attend the health facility is not known.

Despite these limitations, our data provides useful information on PM risks factors and the use of IPTp-SP in rural setting of Cote d'Ivoire.

## CONCLUSION

The identification of risk factors for PM is essential as it will help program managers implement policies that effectively utilize the scarce resources to reduce the burden of the disease. In this study, the prevalence of PM was 7.3% and risks factors of this PM were low parity, residence, lack of usage of LLINs, and maternal peripheral parasitemia.

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## Conflicts of interest

There are no conflicts of interest.

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