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EC GYNAECOLOGY
Research Article

Adverse Clinical and Obstetric Outcomes Associated with Placental Infection by *Plasmodium falciparum* in Luanda-Angola

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Received: March 16, 2017; **Published:** May 17, 2017

Abstract

Introduction: Placental malaria is a complication of malaria in pregnancy and is associated with adverse clinical and obstetric outcomes. This study intends to associate clinical symptoms of malaria and adverse obstetric outcomes with the presence of *Plasmodium falciparum* in the placenta of pregnant women in Luanda, Angola.

Methods: We conducted a hospital based analytic cross-sectional study. Eight hundred and sixty-six women who were in labor and met the inclusion criteria were included in the study. The association between clinical and adverse obstetric outcomes and the presence of parasites in the placenta was analyzed using logistic regression.

Results: *P. falciparum* (diagnosed by PCR) was detected in 143 (16.5%) women. Women who were primigravidae were at an increased risk to have placental malaria (OR = 1.5, CI 1.6 - 2.18). The presence of placental malaria increased the risk of postpartum hemorrhage (OR = 2.6, CI 1.09 - 6.24), premature rupture of membranes (OR = 1.5, CI 1.04 - 2.27) and low placental weight (OR = 1.8, CI 1.20 - 2.73). Placental malaria was significantly associated with gestations (p = 0.01), postpartum hemorrhage (p = 0.03), premature rupture of membranes (p = 0.01) and low placental weight (p = 0.003). Conclusions: Placental malaria due to *P. falciparum* infection was associated with a significant risk of adverse maternal and fetal outcomes in Luanda, Angola.

Keywords: *Placental Malaria; Plasmodium falciparum; Low Birth Weight; Placental Weight; Angola*

Introduction

Placental malaria is a complication of malaria in pregnancy and is associated with adverse outcomes. The adverse maternal and perinatal outcomes classically described by various researchers include abortion, intrauterine growth restriction/small-for-gestational age newborn, preterm birth (< 37 weeks gestation), low birth weight (< 2500g at birth), perinatal death, and congenital infection [1-7]. This disease causes more severe maternal effects, preterm births, and maternal and infant mortality in areas of unstable endemicity or when a non-immune individual acquires malaria [8]. In endemic areas, women have usually acquired sufficient immunity to prevent febrile diseases and are less likely to have preterm births and maternal complications caused by malaria. Nevertheless, asymptomatic pregnant

women remain at risk of anemia, and their fetuses are at risk of intrauterine growth restriction. In a study published in 2012, it was estimated that in endemic areas, approximately 19% of children with low birth weight were from mothers with malaria infection, and 6% of infant deaths were attributed to the low weight associated with malaria. These estimates imply that in the malaria-endemic areas in Africa, 100,000 infant deaths per year may be due to low weight caused by malaria in pregnancy [6]. Factors associated with increased severity of malaria during pregnancy include low parity, low maternal age, non-immune immunological status, infection by the species *P. falciparum*, high parasitemia, placental infection, socio-economic background of the patient, place of residence (rural or urban), and season in which the infection is acquired [9-11]. Of all *Plasmodium* species, infection by *P. falciparum* is the most severe, most likely due to placental sequestration/inflammation and the impact on severe anemia, given that *P. falciparum* has a propensity for mature erythrocytes. *P. falciparum* is associated with a significant risk of maternal and fetal adverse events (e.g., death, anemia, low birth weight) [12-14] and is more common in areas of high endemicity and in primigravidae women [15,16].

Methods

A hospital based cross sectional study was conducted in Luanda, Angola, where *P. falciparum* is responsible for over 90% of all infections [17]. The study was performed in the Lucrecia Paim Maternity Hospital and the Augusto Ngangula Specialized General Hospital, in Luanda, Angola, from April 2006 to February 2008. Eight hundred and eighty-six pregnant women in labor participated in this study, after giving their informed consent. The recruitment and inclusion criteria are detailed in Valente., *et al*. [18] and Campos., *et al* [19]. *Plasmodium falciparum* (by PCR) was detected in 143 (16.5%) of the participants. The detection of parasites in the different tissues was performed as described in Valente., *et al*. [18] and Campos., *et al* [19]. In short, the extraction of parasite DNA from samples of peripheral blood, placenta and umbilical cord blood was performed using phenol-chloroform method. Confirmation of infection by *Plasmodium* and identification of the four species of human malaria were performed on all specimens (peripheral blood, four quadrants of the placenta, and umbilical cord) of all women involved in the study. The identification was performed by a method of "nested" PCR using a pair of primers specific for the genus in the first reaction, followed by four species-specific reactions, as described by Snounou [20]. The amplified DNA products were then analyzed by electrophoresis in a 2% agarose gel that was stained with ethidium bromide and visualized under ultraviolet light.

Data Analysis

The software Epi-Info version 3.5.1 (CDC, Atlanta, USA) was used to perform a descriptive analysis of the results, and the data are presented in tables and as percentages. The Fisher exact test was used for the association between the variables; placental malaria was considered as the dependent variable, and a p value < 0.05 was considered significant (providing confidence intervals of 95%). Multivariate analysis was performed using multinomial logistic regression. Clinical symptoms (i.e., fever, headache, malaise, nausea, vomiting, diarrhea, jaundice and arthralgia), as well as certain adverse outcomes to the pregnancy (i.e., preeclampsia, eclampsia, anemia, rupture of membranes, postpartum hemorrhage, intrauterine death, malformations, newborn weight, and placental weight), were analyzed. The variables were categorized and used as follows: age [< 18 years, 18 - 24 years and > 24 years]; parity: [primiparous (1 birth) and multiparous ≥ 2 births]; place of residence [urban and peri-urban]; birth weight [< 2500 grams and ≥ 2,500 grams]; and placental weight [< 500 grams and ≥ 500 grams]. Anemia was defined as hemoglobin values of < 11 g/dL.

The study protocol was approved by the Ethics Committee of the School of Medicine of the Agostinho Neto University and the Ministry of Health of the Republic of Angola.

Results

General characteristics of the women

From the 866 women included in the study 143 (%) tested positive for *P. falciparum* by PCR (at least one positive compartment). The mean age of the participants was 24 years (SD 6.1). The most predominant age group was 18 - 24 years 384 (44.3%); however, age < 18

years accounted for 13.5%. *P. falciparum* malaria infection was more common in the 18 - 24 years age group (n = 62, 43.4%) but was not statistically significant (p = 0.10). Six hundred and twenty-nine women (72.6%) had primary education or no formal education, while two hundred and thirty-seven (27.4%) had secondary education or higher. With regard to occupation, housewives were predominant 600 (6.3% of cases). Women living in the peri-urban area accounted for 564 (65.1%) of the cases. The socio-demographic characteristics of the individuals are shown in Table 1.

Characteristics	Number	*Plasmodium falciparum*		OR	95% CI	p-Value
		Positive	Negative			
Age group						
< 18 years	117	27 (18,9%)	90 (12,4%)			
18 - 24 years	384	62 (43,4%)	322(44,5%)	-	-	0.10
≥ 25 years	365	54 (37,8%)	311(43%)			
Education level						
None or primary education	629	111(77,6%)	518 (71,6%)			
Secondary education or higher	237	32 (22,4%)	205 (28,4%)	0.7	0.47 - 1.11	0.08
Occupation						
Housewives	600	99 (69.2%)	501 (69.3%)			
Student	157	22 (15.4%)	135 (18.7%)			0.41
Public worker	109	22 (15.4%)	87 (12%)			
Residence						
Urban	302	44 (30,8%)	258 (35,7%)			
Peri-urban	564	99 (69,2%)	465 (64,3%)	0.8	0.54 - 1.17	0.151

Table 1: *Socio-demographic characteristics of women infected with Plasmodium falciparum (n = 866).*

Obstetric characteristics and prevalence of placental malaria

Placental malaria infection was evaluated in the studied women. Of the 866 women, 338 (39%) were primigravidae and 528 (61%) multigravidae. The women had an average 2.6 (SD 1.9) gestations. Of the 866 women, 144 (16.6%) had one or more previous abortions and 722 (83.4%) did not. The results also show that the prevalence of *P. falciparum* malaria infection was higher in primiparous women 62.9% (90), than in multiparous women 37.1% (53).

Characteristics	Number	*Plasmodium falciparum*		OR	95% CI	p-Value
		Positive	Negative			
Gestations						
Primigravidae	338	68(47.6%)	270 (37.3%)			
Multigravidae	528	75 (52.4%)	453 (62.7%)	1.5	1.06 - 2.18	0.01
Parity						
Primiparous	534	90 (62.9%)	444 (61.4%)			
Multiparous	332	53 (37.1%)	279 (38.6%)	1.06	0.73 - 1.54	0.40
Abortion						
Previous abortion	144	25 (17.5%)	119 (16.5%)			
No previous abortion	722	118 (82.5%)	604 (83.5%)	1.07	0.66 - 1.72	0.42

Table 2: *Obstetric characteristics of women infected with Plasmodium falciparum (n = 866).*

Predisposing factors for placental malaria

The clinical manifestations and potential risk factors for placental malaria were studied, and the univariate and multivariate logistic regressions are shown in Tables 3 and 4. Seven of the 143 positive patients reported having had recurrent episodes of fever during the prenatal period. General malaise was also reported by 234 (27%) of the women during pregnancy and of those 29 were positive for P. falciparum. One hundred and twenty (13.9%) of the women reported diarrhea during pregnancy. Women living in urban area were at less risk of contracting placental malaria than the ones who lived in the peri-urban area (OR = 0.8, CI 0.54 - 1.17) however this difference was not statistically significant. Women who were diagnosed with pre-eclampsia and eclampsia were at increased risk of contracting placental malaria (OR = 1.2, CI 0.57 - 2.56) and (OR = 1.6, CI 0.17 - 16.36) respectively, although it was not statistical significant. The same had applied for women with anemia (OR 2.2, CI: 0.69 - 7.51). Women with postpartum hemorrhage were 2.6 more likely to have placental malaria (OR 2.6, CI: 1.09 - 6.24). Two hundred and twenty-one women had premature rupture of the membranes during childbirth, of whom 47 (32.9%) had placental malaria. Placental malaria increased the risk of premature rupture of membranes during labor by 1.5 times but was not significantly associated with it (OR = 1.5, CI 1.04 - 2.27). Intrauterine death were confirmed in 25 of the women of whom six had placental malaria (OR 1.6, CI 0.63 - 4.13). Sixty-six women had newborns with low birth weight (< 2,500 grams), eight of whom had placental malaria. Placental malaria increased the risk of low-birth weight by 1.4 times but was not significantly associated with it (OR = 1.4, CI 0.68 - 3.15). It was also observed that placental malaria increased the risk of low placental weight by 1.8 times with statistically significant association (OR = 1.8, CI 1.20 - 2.73 p = 0.003). Otherwise placental malaria was significantly associated with gestations (p = 0.01), postpartum hemorrhage (p = 0.03) and premature rupture of membranes (p = 0.01).

Characteristics	Number	*Plasmodium falciparum*		OR	95% CI	p-Value
		Positive	Negative			
Fever						
Yes	46	7 (4.9%)	39 (5.4%)			
No	820	136 (95.1%)	684 (94.6%)	0.9	0.39 - 2.06	0.50
Headache						
Yes	284	39 (27.3%)	245 (33.9%)			
No	582	104 (72.7%)	478 (66.1%)	0.7	0.49 - 1.09	0.07
Malaise						
Yes	234	29 (20.3%)	205 (28.4%)			
No	632	114 (79.7%)	518 (71.6%)	0.6	0.41 - 0.99	0.02
Nausea						
Yes	207	30 (21%)	177 (24,5%)			
No	659	113 (79%)	546 (75.5%)	0.8	0.52 - 1.26	0.21
Vomiting						
Yes	231	30 (21%)	201 (27.8%)			
No	635	113 (79%)	522 (72.2%)	0.6	0.44 - 1.06	0.05
Diarrhea						
Yes	120	22 (15.4%)	98 (13.6%)			
No	746	121 (84.6%)	625 (86.4%)	1.1	0.07 - 1.91	0.32
Coma						
Yes	6	1 (0.7%)	5 (0.7%)			
No	860	142 (99.3%)	718 (99.3%)	1.0	0.11 - 8.72	0.66
Preeclampsia						
Yes	47	9 (6.3%)	38 (5.3%)			
No	819	134 (93.7%)	685 (94.7%)	1.2	0.57 - 2.56	0.36

***Table 3**: Predisposing factors for placental malaria (n = 866).*

Characteristics	Number	*Plasmodium falciparum*		OR	95% CI	p-Value
		Positive	Negative			
Eclampsia						
Yes	4	1 (0.7%)	3 (0.4%)			
No	862	142 (99.3%)	720 (99.6%)	1.6	0.17 - 16.36	0.51
Anemia						
Yes	13	4 (2.8%)	9 (1.2%)			
No	853	139 (97.2%)	714 (98.8%)	2.2	0.69 - 7.51	0.15
Hemorrhage						
Yes	24	8 (5.6%)	16 (2.2%)			
No	842	135 (94.4%)	707 (97.8%)	2.6	1.09 - 6.24	0.03
Arthralgia						
Yes	4	1 (0.7%)	3 (0.4%)			
No	862	142 (99.3%)	720 (99.6%)	1.6	0.17 - 16.36	0.51
Rupture of membranes						
Yes	221	47 (32.9%)	174 (24.1%)			
No	645	96 (67.1)	549 (75.9%)	1.5	1.04 - 2.27	0.01
Intrauterine death						
Yes	25	6 (4.2%)	19 (2.6%)			
No	841	137 (95.8%)	704 (97.4%)	1.6	0.63 - 4.13	0.21
Malformations						
Yes	8	1 (0.7%)	7 (1%)			
No	858	142 (99.3%)	716 (99%)	0.7	0.08 - 5.90	0.60
Weight of the Newborn						
< 2500 g	66	8 (5.6%)	58 (8%)			
≥ 2500 g	800	135 (94.4%)	665 (92%)	0.6	0.31 - 1.45	0.20
Weight of the placenta						
< 500 g	172	41 (28.7%)	131 (18.1%)			
≥ 500 g	694	102 (71.3%)	592 (81.9%)	1.8	1.20 - 2.73	0.003

Table 4: *Predisposing factors for placental malaria (n = 866).*

Discussion

Despite having been reported in the literature for the first time over 70 years ago [21], malaria in pregnancy has been a neglected research area. Malaria in pregnancy is often underestimated both as a public health problem and by the clinicians treating individual cases [22]. This study sought to associate adverse obstetric and clinical manifestations with placental malaria in the Augusto Ngangula Specialized General Hospital and in Lucrecia Paim Maternity, located in Luanda, Angola. Every year, 50 million women living in malaria-endemic areas become pregnant; half of them live in Africa [23]. An estimated 10,000 women and 200,000 children die as a result of malaria infection during pregnancy. Human malaria is caused by five species of *Plasmodium: P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi* [1]. The majority of the infections are due to either *P. falciparum* or *P. vivax*, but mixed infections with more than one species of *plasmodium* can also occur. Most deaths related to malaria are due to *P. falciparum*.

In this study, 16.5% women infected by *P. falciparum* at delivery had placental infection. One of the unique features of malaria in pregnancy is the ability of erythrocytes infected by *P. falciparum* to be sequestered in the placentas' intervillous space [24]. The average prevalence of placental malaria in areas of stable transmission is 26%, but it may be even higher when more sensitive methods, such as

histology or polymerase chain reaction (PCR), are used instead of optical microscopy, as was the case with our study [8,25]. The study conducted by a team from the President's Malaria Initiative [26] also found that distance from the city center was a critical malaria susceptibility factor. Among the participants with fever, participants whose health units were located more than 15 km from the city center were almost seven times more likely to have malaria than participants whose health units were within 15 km of the city center. Together, these results indicate that malaria transmission is very low in the urban areas of Luanda but can still be a problem in the outskirts of the city. The clinical manifestations of malaria are nonspecific and variable. Virtually all non-immune individuals have fever, which may be periodic or not. Other common symptoms include chills, malaise, sweating, headache, myalgia, fatigue, nausea, abdominal pain, vomiting, diarrhea, jaundice, and cough [27,28]. In this study, headache, malaise, and diarrhea each showed a statistically significant association with placental malaria [p = 0.037, 0.055 and 0.028, respectively].

Pregnant women infected with *P. falciparum* in areas of high transmission tend to be asymptomatic. In pregnant women, placental infection can be detected even in the absence of peripheral parasitemia. In Tanzania, in an area of stable malaria, no parasites were observed in the maternal bloodstream of 46.3% of the women with histological evidence of placental malaria. If a patient is in this area and shows any febrile symptoms, we should suspect the presence of malaria [29,30]. In this study, fever reported by the participants did not prove to be an indicator of risk of contracting placental malaria.

Women who had premature rupture of membranes, low placental weight and postpartum hemorrhage showed a propensity for placental malaria. In pregnant women with malaria, intrauterine growth restriction and preterm birth contribute to low birth weight. In some areas, malaria was considered responsible for over 70% of intrauterine growth restriction and over 25% of low birth weight [8]. Fetal growth restriction is strongly associated with the presence of parasites in the placenta and the corresponding inflammatory infiltration. It is believed that placental infection leads to the thickening of the placenta and fibrin deposition and hence to decreased placental transport of oxygen and nutrients [15].

A cross-sectional study performed in Malawi with 2.462 pregnant women showed that increasing the number of *P. falciparum* infections during pregnancy increased the risk of low birth weight and maternal anemia [31]. In this study, anemia showed no statistically significant association or risk for placental malaria. Our study examined the association of postpartum hemorrhage (blood loss greater than 400 mL of blood) and placental malaria, noting the existence of risk. A study involving 706 uncomplicated vaginal deliveries that was performed at the Muhimbili University Hospital, Dar es Salaam, Tanzania in 2007 showed that the odds ratio for postpartum hemorrhage (400 mL or more) was significantly increased in women with placental malaria (OR = 3.2, 95% CI 1.1 - 9.0, p = 0.028) [32].

Conclusions

In Luanda, placental malaria due to *P. falciparum* infection was associated with a significant risk of adverse maternal and fetal outcomes and was significantly associated with nonspecific symptoms.

Acknowledgments

We thank the Angolan women, especially the parturients at the Augusto Ngangula Specialized General Hospital and at Lucrecia Paim Maternity Hospital, and their respective directors, who made the study possible.

We also thank Eng. Rodrigues José Capitão Cangangula and Dr Rosa Diogo de Jesus Moreira for their interest in reviewing the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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Volume 4 Issue 4 May 2017