HIGH PREVALENCE OF PLCENTAL MALARIA AND LOW BIRTH WEIGHT IN SAHELIAN PERIURBAN AREA

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Abstract. The impact of placental malaria in African urban areas is poorly documented. We therefore conducted a study during the rainy season in Dakar, an area with low malaria transmission. Two groups of delivering women were enrolled according to the detection of PfHRP2 in placental blood. Ten percent of the women were positive for parasites in the placenta, and microscopic examination showed, respectively, 17%, 22%, and 44% of past, acute, and chronic infection. The mean birth weight decreased drastically with the infection of the placenta (2,684 ± 67 versus 3,085 ± 66 g for controls), particularly with chronic infection. Chronic infection was not linked with parasitemia in maternal venous blood. Seventy-six percent of positive women were anemic (46% of the controls). Severe anemia was also associated with chronic infection. Long-lasting infections are the most deleterious to mother and infant and are most likely associated with drug resistance of parasites.

INTRODUCTION

In highly endemic areas, malaria infection during pregnancy is an important cause of morbidity in mothers who have severe clinical malaria episodes and maternal anemia. It also has adverse consequences for the infant, notably low birth weight (LBW) caused by intra-uterine growth retardation and pre-term delivery.1 In these areas, pregnancy-associated malaria (PM) is more severe in primigravid than in multigravid women. A key feature of PM is the accumulation of P. falciparum–infected erythrocytes (IEs) in the placenta, which is thought to contribute to LBW through impairment of placental circulation and alterations in the physiologic exchanges with the fetus. Parasite sequestration in the placenta is caused by cytoadherence of IEs to placenta-specific surface receptors.2–4 Importantly, antibodies preventing IE cytoadhesion are detected in highly endemic areas, in multigravid women, but not in primigravid or nulliparas, indicating that they likely contribute to protection against placental malaria. In addition to local cytoadherence to the endothelial surface, parasite sequestration in the placenta might also result in slow and low venous flow and accumulation of IEs in the intervillous space.5 However, placental malaria is preventable using efficient chemoprophylaxis during pregnancy, which has been shown to both reduce maternal anemia and to increase birth weight.5

The prevalence of PM is documented in many rural areas of African countries including Senegal.6 In 2004, about 35% of the population of this country are now living in the urban area of Dakar, and this population is rapidly growing. In this area the transmission of malaria is low and seasonal with a distinct interruption during the winter. In this context the immunity of the population against malaria is very low, which can change the parasite-placenta interactions. Is placental malaria a problem of public health in this setting? At the same time very few data are available 1) on the type of infection experienced by these urban pregnant women and 2) on the relationship between the histologic type of infection and LBW or maternal anemia.

To better document PM in this low endemic setting, we conducted a study at the Roi Baudouin Health Center of Guediawaye, located in the peri-urban area of Dakar. We studied the prevalence of placental infection by detection of PfHRP2 in the placental blood, and we classified placentas by histology. We also quantified parasites in contact with the syncytiotrophoblast to analyze the relationship of these parameters with infant birth weight and the clinical status of the mother at delivery.

MATERIALS AND METHODS

The study area includes four districts located North of Dakar: two urban (Pikine, Guediawaye) and two suburban (Thiaroye and Yeumbeul). In these areas, malaria transmission is seasonal and hypo-endemic and usually occurs during the rainy season (July to October). The local entomological inoculation rate is less than 1 infectious bite/person/yr.7 The peak of distribution of monthly prevalence of malaria at delivery was between October to December.8

The enrollment was conducted during the malaria transmission season at Roi Baudouin Health Center (RBHC), an obstetrical reference center, performing more than 7,000 deliveries/yr. The institutional authorities (Ministry of Health, Medicine Faculty) reviewed and approved the research protocol. Women were recruited at delivery. Informed consent was proposed to women fulfilling inclusion criteria (i.e., ≥ 16 years old, inhabiting in the study area for at least 6 months and presenting uncomplicated delivery of live newborn). For all women who gave informed consent, an immunochromatography test (ICT) detecting P. falciparum HRP2 (MaKromed, Johannesburg, South Africa) was carried out on placental blood. All the women with ICT-positive placenta (positive group) were included, as well as 30 women with ICT-negative placenta (control group), matched with the case group for the parity, categorized in “primiparas,” “secundiparas,” and “multiparas.” A standard questionnaire was used to record demographic and clinical information including mother’s age, gravidity, gestational age (determined by the date of last menstrual period and confirmed by morphometric measurement of the uterus during antenatal clinic visits), history of previous malaria episodes, use of anti-malarial drugs, and mosquito nets during pregnancy. Informations about the
newborn included weight, sex, and Apgar scores at 1 and 5 minutes after delivery. Babies were weighed immediately at birth. LBW was defined as less than 2,500 g, and prematurity as gestational age less than 37 weeks. All ICT-positive women received a malaria treatment with chloroquine after delivery. The anemic women received iron and folate supplementation.

At delivery, 5 mL of maternal venous blood was collected from the arm in an EDTA tube. Cord blood sample (5 mL) was collected from the umbilical vein in heparinized tubes immediately after delivery. Placental blood was obtained by infiltrating several placental biopsy samples with a 50-mL syringe containing 1× phosphate buffered saline (PBS) with 50 mmol/L EDTA.

Full blood counts (FBCs) were determined with an automaton Cell Dyn 3200. Women with hemoglobin (Hb) < 11 and < 7 g/dL were classified, respectively, as anemic and severely anemic. Thick and thin blood smears of the peripheral, cord, and placental blood were routinely prepared, stained with Giemsa (Rhoine Poulenc, France), and examined by light microscopy (×1,000). Parasites and leukocytes were both counted and the number of parasites was counted for 100 leukocytes (expressed as percent).

The placenta was maintained at 4°C and transported to the laboratory within 2 hours after delivery. For histologic analysis, four 1-cm³ pieces of tissue were removed from the center of the maternal side of the placenta. The tissue samples were washed in PBS, fixed in 4% buffered formaldehyde for 12 hours at 4°C, and subsequently cryopreserved with 1 and 2 mol/L saccharose. Tissue samples were frozen in liquid nitrogen and stored at −80°C until cryo-sectioned. Micrometer frozen sections were prepared at −30°C using a cryostat (Leica CM1510). Four slides with three sections each were prepared for each placental tissue sample. Two of the slides were stained with May-Grunwald-Giemsa (MGG; Prolabo, France), the two others with hematoxylin-eosin stain (H&E; Prolabo). Placental frozen sections stained with MGG were examined in the same manner as blood smears. Infected erythrocytes (IEs) were counted for every 100 microscopic fields of intervillous area. We evaluate the number of parasites in contact with the cytotrophoblast, by counting ring, pigmented trophozoites and schizonts separately 1) in the intervillous space or 2) apposed to the syncytiotrophoblast. The number of parasites in contact with the syncytiotrophoblast was expressed as the percent of syncytiotrophoblast-associated parasites out of the total number of parasites for 100 microscopic fields. We calculated the percentage of mature parasites in the placenta by using the ratio of “pigmented trophozoites plus schizonts” to the “total number of parasites.” Hemozoin was visualized in placental frozen sections by staining with H&E, viewing under polarization microscopy and categorizing into three classes (abundant, medium, or low). The localization of the pigment was also recorded.

Placental infections were classified according to a previous study. The infection was classified as acute (AI) when only IEs were detected in placental intervillous spaces. The infection was classified as chronic (CI) when IEs and hemozoin were both detected. The infection was classified as past (PI) when only hemozoin was detected in placental tissue and non-infected (NI) when neither IEs nor hemozoin was detected in the placental sections.

Parasitic DNA extraction from blood samples was performed by standard phenol chloroform procedure. In the gene Pfcrt, codon 76 polymorphism was assessed by sequencing exon 2 according to previous study.

Data analyses were conducted using Stata software (version 6.0). Means were compared by Student t test (ST) or by Mann Whitney U test (MW). Percentages were compared using χ² tests (CS) or Fisher exact test when appropriate. Correlations between parameters were studied using the non-parametric Spearman ρ correlation coefficient test. Data were considered significant at P < 0.05, using two-sided significance.

RESULTS

Between September and December, 692 women were screened. Seventy-one (10.2%) pregnant women presented an ICT-positive placenta (age, 24.52 ± 0.80 years; minimum, 16 years; maximum, 43 years). Their mean number of pregnancy was 2.22 (maximum, 10). The mean gestational duration was 40.36 ± 2.77 weeks. Seven percent of infants from positive mothers were premature. The sex ratio of newborns from ICT-positive placentas was 1.27 (Table 1) and had an Apgar score of 9.4 at 5 minutes. The control group did not show significant differences with ICT-positive women for maternal age (25.70 ± 0.95 years), term of pregnancy, prematurity, number of pregnancies (1.93), sex ratio, and Apgar score of the newborns. Eighty-three percent of ICT-positive women declared having taken chloroquine prophylaxis during pregnancy, but only 45% seemed to follow the regimen properly. Older women seemed to take more adequate prophylaxis regimen than younger women. Only 4% of women slept under mosquito nets during their pregnancy.

The correlation between ICT and placental or venous maternal parasitemia is not absolute. Among the 71 participants with ICT-positive placentas, 16 (22.5%) did not present IEs in venous blood and 14 (20%) in placental blood (Table 2). No

<table>
<thead>
<tr>
<th>Parity</th>
<th>No women (%)</th>
<th>Active infection (mean ± SD)</th>
<th>Parasitaemia (mean ± SD)</th>
<th>Adherent parasites (mean ± SD)</th>
<th>Mean age (mean ± SD)</th>
<th>Term of pregnancy (mean ± SD)</th>
<th>Hb (g/dL) (mean ± SD)</th>
<th>Anemia (%)</th>
<th>RR</th>
<th>Asemia</th>
<th>Sex ratio newborn (mean ± SD)</th>
<th>Newborn birth weight (g) (mean ± SD)</th>
<th>LBW</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ICT positive</td>
<td>71 (100)</td>
<td>66</td>
<td>565</td>
<td>20%</td>
<td>24.52 ± 0.80</td>
<td>40.36</td>
<td>9.68 ± 0.36</td>
<td>72</td>
<td>1.54</td>
<td>1.27</td>
<td>2.684 ± 67</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Primigravidae</td>
<td>25 (35)</td>
<td>72</td>
<td>549</td>
<td>27%</td>
<td>20.16 ± 0.60</td>
<td>40.12</td>
<td>9.57 ± 0.40</td>
<td>73</td>
<td>1.57</td>
<td>1.22</td>
<td>2.600 ± 142</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Secondigravidae</td>
<td>25 (35)</td>
<td>68</td>
<td>736</td>
<td>19%</td>
<td>22.12 ± 0.70</td>
<td>40.80</td>
<td>10.07 ± 0.63</td>
<td>75</td>
<td>1.60</td>
<td>1.50</td>
<td>2.730 ± 100</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Multigravidae</td>
<td>21 (30)</td>
<td>57</td>
<td>381</td>
<td>12%</td>
<td>33.00 ± 1.17</td>
<td>40.14</td>
<td>9.33 ± 0.99</td>
<td>66</td>
<td>1.42</td>
<td>1.10</td>
<td>2.714 ± 111</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>30 (100)</td>
<td>0</td>
<td>0</td>
<td>0%</td>
<td>25.70 ± 0.95</td>
<td>40.23</td>
<td>11.21 ± 0.39</td>
<td>46</td>
<td>1.72</td>
<td>3.085 ± 66</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Parasitaemia are calculated as geometric mean for parasite positive samples; adhesion; amount of parasites on syncytiotrophoblast/total amount of parasites on the slide; relative risk (RR) is calculated in reference to the control group; active infection, chronic + acute infection.
women with ICT-negative placentas (control group) presented parasites in blood samples. Venous maternal parasitemia was significantly lower than in placental blood (58% versus 219%; MW, \( P \leq 0.03 \)), but the two parameters remained correlated (\( r = 0.5; \ P \leq 0.0001 \)). In placental and venous blood, no significant decreases of parasitemia were found according to the age of the mother or the number of pregnancies, which argues for poor immunity against parasites.

At a histologic level, chronic infections were more frequent than acute ones: 16 placentas (22%) were classified as acute infections (AIs) and 31 (44%) as chronic infections (CIs; Figure 1A). Hemozoin was detected in only 12 placentas (PI, 17%). Prevalence of CI decreased with the parity (after two

| Number of positive women; parasite counts in cord and maternal venous blood and placental washing blood; number and parasite stages in placenta sections (MGG staining). IE, infected erythrocytes. |

<table>
<thead>
<tr>
<th>Infection class</th>
<th>Venous cord placental blood</th>
<th>Mean blood parasitaemia (IEs/100 leukocytes)</th>
<th>Placental infection (mean IEs in 100 microscopical fields)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Venous</td>
<td>Cord</td>
<td>Placenta blood</td>
</tr>
<tr>
<td>All classes</td>
<td>55 (77%)</td>
<td>2 (3%)</td>
<td>57 (80%)</td>
</tr>
<tr>
<td>AI</td>
<td>15 (94%)</td>
<td>2 (13%)</td>
<td>16 (100%)</td>
</tr>
<tr>
<td>CI</td>
<td>27 (87%)</td>
<td>0 (0%)</td>
<td>24 (77%)</td>
</tr>
<tr>
<td>PI</td>
<td>5 (42%)</td>
<td>0 (0%)</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>NI</td>
<td>8 (67%)</td>
<td>0 (0%)</td>
<td>2 (17%)</td>
</tr>
</tbody>
</table>

FIGURE 1. Micrograph showing placental villous, intervillous (IVS) and intravillous space (ITS). A, Arrows showing infected erythrocytes (IEs) in the IVS (acute infection, May-Grunwald Giemsa stain, original magnification ×400). B, Arrows show hemozoin in the IVS (past infection, hematoxylin-erosin stain, original magnification ×200). C, Arrows show adhesion of IEs onto the syncytiotrophoblast (MGG stain, original magnification ×200). D, Noninfected placenta (arrows showing not infected erythrocytes, MGG stain, original magnification ×200). E, IEs and hemozoin in the IVS (thin arrows: hemozoin in fibrin; thick arrows: IEs; chronic infection, MGG stain, original magnification ×200). This figure appears in color at www.ajtmh.org.
pregnancies, \( P = 0.01 \) and with the age (after 20 years, \( P = 0.03 \)) of the woman (Figure 2). Histologic sections were negative for 12 placentas (17%) of the ICT-positive placentas.

Parasitemia was significantly higher in AIs than in CIs (MW, \( P = 0.001 \)) for all the samples (venous, placental blood, and placental tissue; Table 2). During AI, most of the parasites on the placenta sections (89%) were late stage and 17% of them were stacked onto the cytotrophoblast, which confirms local selective accumulation of mature stages in the placenta. Second, the ratio between parasitemia in venous blood of the mother and in the placenta was not correlated with the percent of syncytiotrophoblast-associated parasites in the placenta, which can argue for two separate sets of parasites in the two compartments as suggested by genotyping of the parasites (M Niang and others, unpublished data). Third, the number of placentas positive for parasites, the placental and venous parasitemia of positive placentas, and the percent of parasites in contact with the syncytiotrophoblast decreased with the number of pregnancies by univariate analysis. Last, detection of hemozoin (Figure 1B and E) was frequent in this series (43 placentas), and it occurred more frequently during the first pregnancy than in subsequent ones (Figure 3A; CS, \( P = 0.02 \)). After two pregnancies and unrelated to the age of the mother, the quantity of hemozoin pigment detected decreased in placental cells (65% to 35% of cells; CS, \( P = 0.0005 \); Figure 3B).

During this study, we found a high rate of anemia. Seventy-six percent of ICT-positive and 46% of control women were anemic (\( P = 0.01 \); Table 1). Severe anemia was observed in 14% of positive women versus 3% in control women (\( P = 0.01 \)). Once again, the prevalence of anemia decreased with the number of pregnancies (primigravid, 73% versus multigravid 66%; not significant) but not with the age of the mother. The level of hemoglobin in the blood was not related to parasitemia (venous, placental). However, no difference was observed between ICT-positive women with no histologic signs of placental infection and the control groups for the prevalence of anemia.

One of four ICT-positive women had an increased leukocyte count in venous blood (leukocytes > 10,000/\( \mu L \); Figure 4). Blood cell counts differed significantly between ICT-positive and controls women (MW, \( P = 0.0006 \) for leukocytes, \( P = 0.006 \) for neutrophils, \( P = 0.02 \) for monocytes, and \( P = 0.0001 \) for lymphocytes). In venous maternal blood, counts of eosinophils, monocytes, neutrophils, lymphocytes, and platelets were negatively correlated with placental parasitemia. When parasites are present in the venous maternal blood, the situation is more complex and looks like that of a malaria attack. Parasitemia in venous maternal blood was positively correlated with eosinophil counts (\( r = 0.47, P = 0.003 \)) and negatively correlated with platelet (\( r = -0.46, P = 0.004 \)), lymphocyte (\( r = -0.33, P = 0.04 \)), and neutrophil counts (\( r = -0.48, P = 0.002 \)). Monocyte counts were inversely related to hemoglobin levels (\( r = -0.35, P = 0.04 \)).

The presence of parasites has a negative impact on the development of the fetus. The mean newborn birth weight was lower for ICT-positive women (2,684 ± 67 g; minimum, 1,000 g; maximum, 3,750 g) compared with control uninfected women (3,085 ± 66 g; minimum, 2,600 g; maximum, 3,900 g; MW, \( P = 0.003 \); Table 1). As in other areas of transmission,
PLACENTAL MALARIA IN SAHELIAN PERIURBAN AREA

According to the national census of 2004 (ESIS-Ministry of Health), of the 140,000 pregnancies registered each year in Senegal, about 50,000 women delivered in the Dakar area, and 12% of newborns were less than 2.5 kg. These LBW newborns are a major target group for national health policy, but to date, this issue has been poorly studied. In our study, 10% of the women presented an ICT-positive placenta. This prevalence is rather high according to the transmission level. These data confirm a preliminary report, but align more with a stable transmission context. This confirms that, in low transmission areas, placental malaria is a frequent disease. One half of the ICT-positive women were young women, and most of them had less than three pregnancies.

In this study, the major adverse outcomes of malaria infection were LBW and anemia, but not preterm delivery, as described in stable transmission areas. In rural areas, other factors such as field labor could also associate with malaria to induce preterm delivery.

In this study, histologic sections were negative for 17% of the ICT-positive placentas. Eighty-seven percent of the women with parasites in the placenta had positive venous blood, which was in agreement with other low transmission areas and could be related to a low level of immunity. Parity and age of the mother. PigMo, in monocytes; Pigvil, within villous; Pig0, no hemozoin.

the time of infection had a major impact on mean birth weight: 2,558.8 ± 120.9, 2,605.4 ± 132.3, 2,790.6 ± 121.8, and 2,925.4 ± 120.7 g for the CI, PI, AI, and NI groups, respectively. Overall, long-term infections (CI and PI) were significantly more deleterious for newborns than AI or NI with 50% and 32% of LBW, respectively. Actual parasitemia had less importance in this process, because birth weight was unrelated to venous, cord, or placental parasitemia or to parasite counts within the placental tissue. Lower birth weight was associated with the presence of hemozoin in the placenta (2,847 ± 439 versus 2,572 ± 629 g; LBW, 23% versus 42%).

Birth weight was positively correlated with hemoglobin level at delivery (Spear, r = 0.26, P = 0.03) and negatively correlated with eosinophil (r = −0.26, P = 0.02) or monocyte counts in peripheral blood (r = −0.26, P = 0.03). There was no impact of the class of infection, age, or parity of the women on the term of delivery (Table 1).

Sequences of PfCRT-exon 2 were obtained for 54 venous samples. Isolates (85.7%) presented a K to T mutation of codon 76. The presence of the mutation was not correlated with presumably adequate chemoprophylaxis.

FIGURE 3. Relationship between hemozoin in placenta and gravidity. A. Relationship between quantity of hemozoin and gravidity. Pig0, no hemozoin; Pig1, hemozoin medium; Pig2, hemozoin abundant. B and C. Localization of hemozoin on slide, according to parity and age of the mother. PigMo, in monocytes; Pigvil, within villous; Pig0, no hemozoin.

DISCUSSION

Most of the parasites in these placentas were mature, which suggests a selective accumulation of the mature stages as described previously.

In our group, hemozoin was observed in 60.5% of the ICT-positive placentas. It was detected within host monocyte/macrophages after parasite clearance. As in other low transmission areas, it represents a sensitive marker of malarial infection even in absence of the parasite. The presence of hemozoin in the placenta was more frequent during the first pregnancy than in subsequent pregnancies. This decay was not related to age and confirms the role of parity. Presence of hemozoin was also associated with a significant reduction in birth weight and with maternal anemia. This is not in agreement with other studies conducted in stable transmission areas. In our data, prevalence of LBW correlated with both hemozoin and monocyte counts, which support this detrimental effect of inflammation.

During this study, we found a high level of anemia, despite the national policy to supply women with folicates and iron and a greater number of antenatal visits. This confirms that malaria is a major cause of anemia even in urban areas. Prevalence of anemia was higher in primiparas than in multiparas.
infected women, despite the age of the mother. Hemoglobin level was unrelated to parasite counts in venous blood or placenta, which is in contradiction with studies conducted in areas of stable transmission. Placental infection was associated with a decrease in venous eosinophils, monocytes, neutrophils, lymphocytes, and platelets counts. Monocyte counts were inversely related to hemoglobin level.

Placental malaria was also associated with lower birth weight. Thirty percent of the newborns had a LBW in the ICT-positive group in agreement with a previous study and in other settings in Africa. Because the prevalence of LBW is 12% in this area, 1,500 LBW infants can be attributed to malaria each year in Dakar. This result is not different from that observed in areas of stable malaria transmission and fits with the meta-analysis of Brabin and others. However, in Dakar, LBW was unrelated to venous, cord, or placental parasitemia or to parasite counts within the placental tissue as it is observed in stable transmission area. It was mainly associated with the presence of hemoszoin in the placenta and with an increase in eosinophil or monocyte counts in maternal blood. In our epidemiologic setting, long-term infections and inflammation were significantly more deleterious for newborns and the mother than acute infections. This situation is not improved by chemoprophylaxis because even self-declaring complete chemoprophylaxis was not associated with a better outcome of the pregnancy.

Analysis of the PfcrT gene of the strain collected in the blood confirmed that most of the isolates presented a K to T of mutation codon 76. A usual ratio of 1.3 is used to correlate the rate of PfcrT mutation and the rate of chloroquine resistance in West Africa. Thus, 65% of the parasite isolates in these women may be chloroquine resistant, which confirms the ineffectiveness of the chloroquine-based prophylaxis strategy for this area as recently described in Senegal.

In summary, primipara women with malaria infection and placental hemoszoin pigment had infants with lower birth weight. Even in this area of low transmission, placental parasite densities and numbers of IE's in contact with the cytotrophoblast decreased after the second pregnancy. However, in this peri-urban setting, chronic and past placental infections were associated with maternal anemia and LBW, regardless of term of delivery or the number of pregnancies. Despite a low level of transmission in urban Dakar, LBW induced by malaria is a real health problem not controlled by chloroquine prophylaxis. The age of the mother had no impact on all the parameters registered, which suggests poor immunity against parasites. This is in agreement with the low level of transmission in this area and can explain the high prevalence of placental malaria observed. The high rate of mutations observed on PfcrT also indicates a high level of drug resistance of placental parasites, which can also explain this prevalence. The duration of the infection was found to be more deleterious than the level of parasitemia, and no correlation was found between cytoadhesion of parasites and parasitemia with the
outcome of the pregnancy. Therefore, the impact of a vaccine targeting parasite adhesion can be questioned. The most important factor would be to reduce duration of parasite infection, which is the aim of the Intermittent Preventive Treatment strategy (IPT). IPT has shown its efficiency at reducing maternal anemia, pre-term delivery, and LBW in numerous settings, as long as local parasite resistance to the drug is low. This can not be true for a long time in this ever-changing urban setting.

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