The Impact of Placental Malaria on Gestational Age and Birth Weight

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Maternal malaria is associated with reduced birth weight, which is thought to be effected through placental insufficiency, which leads to intrauterine growth retardation (IUGR). The impact of malaria on preterm delivery is unclear. The effects of placental malaria–related changes on birth weight and gestational age were studied in 1177 mothers (and their newborns) from Tanzania. Evidence of malaria infection was found in 75.5% of placental samples. Only massive mononuclear intervillous inflammatory infiltration (MMI) was associated with increased risk of low birth weight (odds ratio [OR], 4.0). Maternal parasitized red blood cells and perivillous fibrin deposition both were associated independently with increased risk of premature delivery (OR, 3.2; OR, 2.1, respectively). MMI is an important mechanism in the pathogenesis of IUGR in malaria-infected placentas. This study also shows that placental malaria causes prematurity even in high-transmission areas. The impact of maternal malaria on infant mortality may be greater than was thought previously.

Despite recommendations that malaria be controlled among pregnant women in endemic areas [1], malaria during pregnancy remains a significant cause of maternal and infant mortality and morbidity. Problems related to compliance with drug regimens and the use of partially effective antimalarials are some of the reasons that have led many countries to question, and in many cases abandon, malaria control for pregnant women.

The parity pattern of malaria susceptibility in highly endemic areas (whereby primigravidae and, to a lesser extent, secundigravidae are more affected than are other parities) has been well established [2]. The tendency of *Plasmodium falciparum* parasites to invade the placenta in semi-immune women also has been described [3]. Regardless of the level of endemicity, the main effects of malaria during pregnancy are maternal anemia and reduced birth weight of the newborn [4–6].

Malaria is thought to reduce birth weight through a combination of systemic and local effects. First, malaria may affect birth weight through malaria-induced anemia. Second, malaria also may reduce birth weight through placental infection [7]. In this case, parasites either directly cause a mechanical compromise of placental circulation or indirectly interfere with placental functions and/or induce pathological lesions [8, 9]. However, there is still no agreement on which are the main mechanisms that mediate reductions in birth weight in placental malaria.

Both malaria-induced anemia and placental malaria are thought to mediate reductions in birth weight primarily through intrauterine growth retardation (IUGR) [10]. Overall, there are few reports on the association between malaria in pregnancy and gestational age. This evidence often is conflicting. Although high rates of premature deliveries and abortions have been reported during malaria epidemics [11], a study from an area of unstable mesoendemic transmission did not show an effect of maternal malaria on gestational age [12]. There also are conflicting results among semi-immune women; most studies involving such women have failed to show a difference in the proportion of preterm deliveries among infected and noninfected mothers [13, 14], but 2 recent reports suggest that malaria may lead to prematurity [15, 16].

Most reports on the prevalence of placental malaria and its

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On admission to the hospital for delivery, a copy of the consent letter (which included detailed information on procedures and potential risks and benefits of the study), written in Kiswahili, was given to the mother. This letter was then read to the mother by a project clinical officer, who answered any questions the mother might have. After checking (using pre-established key questions) to verify that the mother understood all implications, the mother was invited to sign the consent form.

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impact on the outcome of pregnancy come from areas of low, moderate, or high but seasonal transmission [2, 15–18]. Very little is known about high– and perennial–malaria transmission areas, where most women are exposed throughout the course of their pregnancies. To improve our understanding of the pathophysiology of placental malaria–related low birth weight (LBW) and of the epidemiology of maternal malaria, we studied the impact of malaria-associated placental changes on birth weight in a highly endemic area of southern Tanzania. Specifically, we have attempted to determine the impact of placental malaria on IUGR and gestational age.

Materials and Methods

Study area and population. Our study was undertaken in the town of Ifakara (Kilombero District) in southeastern Tanzania. The characteristics of the area have been described elsewhere [19]. In brief, the population of Ifakara is estimated to be 50,000. Most villagers are subsistence farmers who grow rice and maize, and there also is an increasing number of small traders. There are 2 rainy seasons and a cool, dry season.

P. falciparum malaria transmission is intense and perennial, with an average entomological inoculation rate of ~300 bites per person per year in a nearby village [20]. Chloroquine consumption is high, although 60% of parasite strains show resistance at day 7 [21]. The National Malaria Control Programme recommends routine malaria chemoprophylaxis to all pregnant women. However, in the Kilombero District, such chemoprophylaxis rarely takes place. Government health facilities in Ifakara are limited to the St. Francis Designated District Hospital (SFDDH), a 375-bed hospital, and the adjacent maternal and child health clinic. More than 60% of pregnant women from Ifakara deliver their newborns at SFDDH (F. Font, R. Natham, H. Mansanja, M. Alonso, L. L. Quinto, and P. L. Alonso, unpublished data).

Sample collection. During a 12-month period (November 1994 to October 1995), all women who delivered at SFDDH and who gave their informed consent were enrolled in the study. At delivery, 5 mL of maternal and cord blood was collected into EDTA tubes for hematological assessment, and 2 thick blood smears were prepared for parasitological examination. A placental biopsy specimen was taken from the maternal surface, at an off-center position, and immediately was placed in a plastic container with 10% buffered formalin. The birth weight of the baby was recorded, and the length and head circumference were measured. Within 24 h of birth, the gestational age was assessed using the Dubowitz method [22]. Demographic characteristics of the mother and a brief parity history were recorded at the time of discharge from the hospital.

Classification of birth weight. For the purpose of this analysis, newborns have been classified as normal birth weight (≥2500 g, regardless of gestational age) or LBW (<2500 g). LBW may be due to prematurity, IUGR, or both. However, the accurate identification of IUGR among preterm infants requires ultrasound examination, and this measurement must be supported by the birthweight standards for the population. Because neither of the above measurements were available for our population, LBW babies were further classified as premature-LBW (<2500 g and <37 weeks in gestation) or IUGR-LBW (<2500 g and ≥37 weeks in gestation), as suggested by Steketee et al. [15]. Among the premature babies, only 2 could be classified as growth retarded (according to the definition of a birth weight that is <2 SDs of the mean for the estimated gestational age). These babies were categorized as premature-LBW in our analysis. In addition, 39 normal birth weight infants were classified as premature; they were included in all analyses except the analysis of gestational age among LBW babies.

Laboratory methods. Placental biopsy specimens were stored at 4°C until they were transported for use in histopathological studies, which were done at 1–3 months after biopsy. The samples were processed using standard methods, whereby 4-μm sections were stained with hematoxylin and eosin, Giemsa's stain, and periodic acid–Schiff reagent. Sections also were examined under polarized light to assess the deposition of malarial pigment. Placentas were classified into 4 categories on the basis of the presence or absence of parasites and/or pigment. Details of the histological classification are provided elsewhere [23]. In brief, placentas were classified as "not infected" if there was no evidence of parasites or pigment; as "acute infection" if there were parasites and absent or minimal pigment deposition within fibrin; as "chronic infection" if there were parasites and a significant amount of pigment deposition; and as "past infection" if there was pigment but no parasites.

Statistical methods. Univariate analysis and multivariate linear and logistic regression models, depending on whether the dependent variables were taken as continuous or categorical, were used to analyze the effect of placental infection and of histological features (as explanatory variables for birth weight, gestational age, and retarded growth). For the multivariate analysis, the independent predictors were selected using a forward stepwise procedure, with an inclusion criterion of $P < .05$ and a removal criterion of $P > .1$. Multivariate analysis was done by adjusting for parity and human immunodeficiency virus (HIV) maternal status. Statistical analysis was done using Stata version 5.0 (StataCorp, College Station, Texas) software.

Results

One thousand two hundred twenty-five women and their live-born singleton infants were enrolled in the study. Birth weight was recorded for 1177 newborns, and gestational age was assessed for 910 (77.3%) of these newborns. Placental samples were collected from 1207 women, and histological studies were done for 1179 of the samples. Eight hundred ninety placental samples (75.5%) showed some evidence of malarial infection. One hundred twelve samples (9.5%) had parasites only, 475 (40.3%) had pigment only, and 303 (25.7%) had both parasites and pigment [23].

Birth weight, LBW, and placental malaria histology. Mean birth weight in the study sample of 1177 babies was 2818.7 g (SD, 429 g). The incidence of LBW babies (<2500 g) was 18% (n = 207). Parity and maternal HIV status were both associated with LBW. Primigravidae had a >3-fold increased risk (odds ratio [OR], 3.6; 95% confidence interval [CI], 2.5–5.2) of having an LBW infant than did women of other parity groups. The prevalence of HIV status was 61 (6.8%) of 897 mothers. HIV-positive women had nearly twice as great a risk of having an

Table 1. Placental findings associated with a risk for low birth weight, in both univariate and multivariate analyses (adjusted for parity and HIV status).

Placental findings	%	OR (95% CI), univariate analysis	OR (95% CI), multivariate analysis[a]
Mononuclear intervellositis			
No	77.6	1.0	
Moderate	16.1	1.8 (1.3–2.7)[b]	1.3 (0.8–2.1)
Massive	6.3	7.0 (4.3–11.5)[c]	4.0 (2.3–7.1)[c]
PLMN			
Normal	92.2	1.0	
Increased	7.8	4.0 (2.6–6.3)[c]	
PRBC			
0%	64.8	1.0	
⩽10%	26.2	1.2 (0.8–1.7)	
>10%	9.0	4.9 (3.2–7.6)[c]	
Pigment			
No	24.6	1.0	
Minimal	37.3	0.7 (0.5–1.1)	
Moderate	24.7	1.4 (0.9–1.8)	
Severe	13.4	3.3 (2.1–5.2)[c]	
Placental infection			
No	24.6	1.0	
Acute	9.5	0.6 (0.3–1.2)	
Chronic	25.6	2.4 (1.6–3.6)[c]	
Past	40.3	0.9 (0.6–1.4)	

NOTE. HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval; PLMN, polymorphonuclear leukocytes; PRBC, parasitized red blood cells.

[a] $n = 1177$.

[b] $P < .01$.

[c] $P < .001$.

LBW baby as did HIV-seronegative mothers (OR, 1.9; 95% CI, 1.1–3.7).

Table 1 shows the placental characteristics associated with the risk of having a baby with a weight of <2500 g, in univariate and multivariate analyses that have been adjusted for parity and HIV maternal status. Only the presence of massive mononuclear intervillositis (MMI) (defined as the presence of moderately or highly increased mononuclear infiltration) was associated independently with a significant increase in the risk of LBW. Pigment deposition significantly affected birth weight in the univariate analysis; this effect was more marked when it was located on the syncytiothrophoblast. Mean birth weight was significantly reduced by >140 g (95% CI, −197.0 to −87.8) when even minimal amounts of pigment were deposited in this location. Interestingly, the effect of maternal parasitized red blood cells (PRBCs) on the baby's birth weight was not statistically significant when it was included in the multivariate model (table 1). The presence of focal calcifications in the mother's stroma significantly reduced the probability that the mother would have an LBW baby (OR, 0.4; 95% CI, 0.2–0.7). When the risk factors associated with a reduction in mean birth weight were analyzed, the same variables were identified. MMI was associated with an average reduction in birth weight of nearly 400 g (95% CI, −494.4 to −296.6).

Gestational age, prematurity, and placental malaria histology. Mean gestational age of the 910 babies assessed was 38.9 weeks (SD, 1.4 weeks). Seventy-two (8%) of the 910 babies for whom gestational age was assessed were preterm (<37 weeks). The proportion of preterm babies was greater among primigravidae than in other parity groups (12.1% vs. 6.0% and 5.5% in gravida 2–4 and 5+, respectively; $P < .01$). HIV maternal status was not associated with an increased risk for prematurity (3.3% vs. 8.1%; $P = .2$).

Table 2 shows the histological changes that were associated significantly with an increased risk of prematurity, in univariate and multivariate analyses. The presence of PRBCs and perivillous fibrin deposition were associated with an independent increased risk of prematurity (OR, 3.2, and 95% CI, 1.5–7.0; OR, 2.1, and 95% CI, 1.3–3.5, respectively). The same risk factors were associated with a significant reduction in mean gestational age. The latter was reduced by nearly a week in the presence of high-density PRBCs (95% CI, −1.2 to −0.5 weeks).

IUGR and prematurity among LBW newborns and their relation to placental malaria. Among the 155 LBW babies for whom gestational age was assessed (75% of the total), 33 (21%) were preterm and 122 (78.8%) were classified as IUGR. Table 3 shows the placental findings associated with the risk for IUGR-LBW, in a univariate analysis. Only MMI is associated

Table 2. Placental findings associated with a risk for prematurity, in both univariate and multivariate analyses (adjusted for parity and HIV status).

Placental findings	%	OR (95% CI), univariate analysis	OR (95% CI), multivariate analysis[a]
Mononuclear intervellositis			
No	78.0	1.0	
Moderate	15.7	1.2 (0.6–2.3)	
Massive	6.3	2.8 (1.3–5.9)[b]	
PLMN			
Normal	91.4	1.0	
Increased	8.6	3.2 (1.7–6.0)[c]	
PRBC			
0%	65.3	1.0	
⩽10%	26.7	2.0 (1.1–3.4)[d]	1.9 (1.1–3.4)[d]
>10%	8.0	4.1 (2.1–8.1)[c]	3.2 (1.5–7.0)[b]
Pigment			
No	24.6	1.0	
Minimal	36.4	1.3 (0.6–2.7)	
Moderate	26.5	1.7 (0.8–3.6)	
Severe	12.5	4.6 (2.2–9.9)[c]	
Fibrin			
⩽30%	84.8	1.0	
>30%	15.2	2.1 (1.2–3.7)[b]	2.1 (1.3–3.5)[b]
BMT			
Normal	77.0	1.0	
Focal	22.0	1.2 (0.7–2.1)	
Diffuse	1.0	10.2 (2.7–39.1)[c]	
Placental infection			
No	24.6	1.0	
Acute	8.5	1.6 (0.6–4.6)	
Chronic	26.1	3.1 (1.4–6.2)[b]	
Past	40.8	1.2 (0.6–2.6)	

NOTE. HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval; PLMN, polymorphonuclear leukocytes; PRBC, parasitized red blood cells; BMT, basal membrane thickening.

[a] $n = 910$.

[b] $P < .01$.

[c] $P < .001$.

[d] $P < .05$.

Table 3. Placental findings associated with intrauterine growth retardation–low birth weight (IUGR-LBW) and preterm-LBW, in a univariate analysis.

Placental findings	IUGR-LBW (n = 122) OR (95% CI), univariate analysis	Preterm-LBW (n = 33) OR (95% CI), univariate analysis
Mononuclear intervellositis		
No	1.0	1.0
Moderate	1.8 (1.1–2.9)[a]	1.6 (0.6–3.9)
Massive	7.4 (4.1–13.5)[b]	5.6 (2.3–15.7)[b]
PLMN		
Normal	1.0	1.0
Increased	3.3 (1.9–5.7)[b]	3.2 (1.3–8.1)[a]
PRBC		
0%	1.0	1.0
⩽10%	1.1 (0.7–1.7)	2.0 (0.9–4.4)
>10%	4.8 (2.8–8.5)[b]	7.5 (3.0–19.0)[b]
Pigment		
No	1.0	1.0
Minimal	0.5 (0.3–0.8)[c]	1.6 (0.5–5.1)
Moderate	1.1 (0.7–1.9)	1.9 (0.6–6.5)
Severe	2.3 (1.3–4.1)[c]	7.0 (2.2–22.6)[c]
Fibrin		
⩽30%	1.0	1.0
>30%	0.7 (0.4–1.2)	3.7 (1.8–7.6)[b]
Calcifications		
Normal	1.0	1.0
Focal	0.3 (0.1–0.6)[c]	0.6 (0.2–1.7)
Moderate	0.6 (0.3–1.2)	0.3 (0.1–1.9)
Placental infection		
No	1.0	1.0
Acute	0.3 (0.1–0.8)[a]	2.7 (0.7–11.0)
Chronic	1.7 (1.1–2.8)[a]	4.1 (1.3–12.6)[a]
Past	0.7 (0.4–1.1)	1.4 (0.4–4.7)

NOTE. OR, odds ratio; CI, confidence interval; PLMN, polymorphonuclear leukocytes; PRBC, parasitized red blood cells.

[a] $P < .05$.

[b] $P < .001$.

[c] $P < .01$.

independently with an increased risk of IUGR-LBW (OR, 4.04; 95% CI, 2.1–7.8). Focal calcifications in the stroma were associated with a reduced risk of IUGR-LBW (OR, 0.3; 95% CI, 0.1–0.6).

Table 3 also shows the univariate analysis of the placental histological features associated with preterm LBW. Of all these variables, only high density of PRBCs (OR, 6.3; 95% CI, 2.2–18.2) and severe fibrin deposition (OR, 3.03; 95% CI, 1.4–6.7) remained significantly associated with an increased risk of preterm LBW, in the multiple regression model.

Anthropometric indices in relation to placental malaria. Chronic malaria infection of the placenta was associated with significant reductions in mean head circumference, length, and body index (weight/length^2) ($P < .001$), whereas past infections were associated with reduced mean length at birth only ($P < .05$) (table 4).

Discussion

Nearly 1 in 5 children born in this highly malaria-endemic area of Tanzania had an LBW, and >20% of these children were born prematurely. Contrary to previous thinking [13, 14, 24], this study shows that placental malaria, even in women living in high-transmission areas, increases the risk of prematurity. The risk of giving birth to a premature baby was >3 times higher if >10% of the red cells in the placenta were parasitized. The fact that maternal PRBCs, not pigment deposition, were related independently to an increased risk of preterm babies suggests that acute and severe infections late during gestation may carry a high risk for resulting in premature delivery. This also is consistent with a report in which cord-blood parasitemia was associated with preterm LBW, since cord-blood parasitemia usually correlates with high-density PRBCs [15]. To our knowledge, this study represents the first instance in which malaria-related histological placental findings have been associated with a significant increased risk of premature delivery and a reduction of mean gestational age.

We recently have described that some malaria-infected placentas may present with features that are similar to the condition called massive chronic intervillositis, and these placentas are associated with a significant reduction in birth weight and gestational age [25]. The results of this study show that inflammatory infiltration of the intervillous spaces was associated with a reduction in birth weight by nearly 0.5 kg, particularly when mononuclear cells were highly increased. The presence of MMI in the placenta also was associated with a 4-fold increase in the risk of LBW. These findings strongly indicate that placental insufficiency attributable to physical blockage by PRBCs [10] may not be the only, or indeed even the most important, mechanism mediating IUGR. This massive monocyte infiltration of the intervillous spaces is likely to be a source of cytokines, including interferon-γ, interleukin-2, interleukin-6, and tumor necrosis factor–α, which are considered detrimental to pregnancy because they are associated with spontaneous abortion, premature labor, and growth retardation [26, 27]. These findings are, therefore, in line with recent observations that cytokine production in the placenta is increased in association with malaria infection [28] and is associated with poor pregnancy outcomes [28, 29].

The significance of pigment deposition in the placenta has long been debated. In our study, pigment deposition was not associated with a significant birth-weight reduction when the analysis was adjusted for parity. This lack of association re-

Table 4. Mean head circumference (HC), length, and body mass index (BMI) of the newborn infant, by category of placental infection.

Placental infection	n	HC (cm), mean ± SD	Length (cm), mean ± SD	BMI (g/cm^2), mean ± SD
No	283	34.4 ± 1.37	48.6 ± 1.69	1.23 ± 0.14
Acute	112	34.3 ± 1.13	48.3 ± 2.14	1.24 ± 0.16
Chronic	301	33.7 ± 1.44[a]	47.9 ± 1.97[a]	1.17 ± 0.15[a]
Past	470	34.2 ± 1.36	48.2 ± 1.90[b]	1.23 ± 0.15

[a] $P < .001$.

[b] $P < .05$.

inforces the suggestion that pigment is an indicator of the severity of the recent active infection rather than a variable that has a direct detrimental effect on fetal growth. In the absence of parasites, pigment deposition was not accompanied by inflammatory infiltration, which reinforces the suggestion that pigment is a rather inert substance [23]. In general, the association between pigment and birth weight was not affected by the location of the pigment, except in the case of the syncytiotrophoblast. Pigment in this site may reflect a severe infection, possibly accompanied by inflammation, in the layer that is in closest contact with fetal circulation, and this pigment possibly has the greatest potential to interfere with intrauterine growth.

Chronic infection of the placenta (with pigment and parasites) appears to be associated with a significant reduction in birth weight and with the risk of LBW, both through prematurity and IUGR. Chronically infected placentas were seen more frequently among primigravidae than among other parities, which suggests either an increased frequency of infections or an impaired ability to resolve them among first gravidae [30]. Meanwhile, acute infections were associated with a statistically significant lower risk of LBW as a result of IUGR and with a nonsignificant increase in the risk of LBW as a result of prematurity. This indicates that acute infections at the end of gestation may play a role in the induction of premature labor, and this indication is in keeping with early reports of abortions and preterm deliveries during malaria epidemics [11]. Chronic infections also were associated with a reduction in the length and head circumference of the babies, indicating a prolonged effect on fetal nutrition, which has been suggested in other studies [6, 31]. Similarly, reduction in the body mass index may reflect the severity and duration of fetal malnutrition.

In conclusion, the histological changes associated with birthweight reduction in relation to malaria have been studied in a large series of placental samples from an area of intense and perennial transmission, where a high percentage of patients show evidence of malaria infection. Our findings allude to mononuclear inflammatory infiltration of the intervillous spaces as the main mechanism to explain malaria-related birthweight reduction, especially growth retardation. Our findings also confirm that malaria infection through placental parasitization in semi-immune women contributes to LBW through prematurity. Given that premature infants are more likely to die than are IUGR babies [32], we conclude that the impact of maternal malaria on infant mortality and morbidity may be greater than previously thought.

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