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A cohort study of *Plasmodium falciparum* malaria in pregnancy and associations with uteroplacental blood flow and fetal anthropometrics in Kenya

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Abstract

Objective—To use ultrasound to explore the impact of malaria in pregnancy on fetal growth and newborn outcomes among a cohort of women enrolled in an intermittent presumptive treatment in pregnancy (IPTp) with sulfadoxine/pyrimethamine (SP) program in coastal Kenya.

Methods—Enrolled women were tested for malaria at first prenatal care visit, and physical and ultrasound examinations were performed. In total, 477 women who had term, live births had malaria tested at delivery and their birth outcomes assessed, and were included in the study.

Results—Peripheral malaria was detected via polymerase chain reaction among 10.9% (n=87) at first prenatal care visit and 8.8% (n=36) at delivery. Insecticide-treated bed nets (ITNs) were used by 73.6% (n=583) and were associated with decreased malaria risk. There was a trend for impaired fetal growth and placental blood flow in malaria-infected women in the second trimester,

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Conflict of interest
The authors have no conflicts of interest.

but not later in pregnancy. Among women with low body mass index (BMI), malaria was associated with reduced birth weight (*P*=0.04); anthropometric measures were similar otherwise.

Conclusion—With IPTp-SP and ITNs, malaria in pregnancy was associated with transient differences in utero, and reduced birth weight was restricted to those with low BMI.

Keywords

Fetal growth; Malaria in pregnancy; Sub-Saharan Africa

1. Introduction

Malaria in pregnancy causes low birth weight, a major contributor to neonatal mortality and morbidity worldwide [1–5]. In Sub-Saharan Africa, where malaria is endemic, malaria in pregnancy may contribute to 25% of low birth weight [6]. However, with enhanced malaria control efforts, malaria incidence is falling in many countries [6].

Other factors modify the effect of malaria on the developing fetus. The risk of decreased birth weight is generally highest among primigravid women, who may experience more severe clinical illness associated with malaria infection [1,2,7]. Additionally, a recent study suggested an interaction between maternal undernutrition and malaria [8]. There is conflicting evidence about how the time of infection during pregnancy affects birth outcomes [8–13]. Some have suggested that first- or second-trimester infection increases risk of low birth weight compared with later infection [10]. However, other studies found that malaria infection late in pregnancy, when fetal weight gain is most rapid, correlated with decreased birth weight [11,12].

Studies of malaria in pregnancy utilizing ultrasound, a method to establish gestational age and fetal growth, have been limited [8,13–15]. In addition to evaluation of fetal growth, ultrasound assesses uterine and umbilical blood flow, both of which may be impaired by malaria in pregnancy [13]. With limited availability of routine ultrasound in Sub-Saharan Africa, few reports have described fetal growth and impairment associated with malaria by ultrasound. One study of 3779 pregnant women from the Thai–Burmese border found that early malaria infection (<24 weeks) was associated with decreased biparietal diameter [14]. Another recent study in Tanzania found that early malaria infection was associated with reduced third-trimester fetal growth [15]. Additionally, in the Democratic Republic of the Congo, ultrasound evaluations established intrauterine growth restriction (IUGR) among women with malaria [8], and significantly increased uterine and umbilical artery resistance among malaria-positive compared with malaria-negative pregnant women [13]. Umbilical artery resistance has been associated with impaired fetal growth and IUGR [16].

In 2004, WHO recommended intermittent preventive treatment (IPTp) with 2 doses of sulfadoxine/pyrimethamine (SP) beginning the second trimester for pregnant women residing in malaria-endemic areas [17,18]; more recent guidelines recommend monthly SP treatment [19]. With increased SP availability, many countries in Sub-Saharan Africa have implemented programs based on the IPTp-SP strategy, and evaluation efforts have been undertaken [6,20–23]. However, a better understanding of factors related to the impact of

malaria on birth outcomes is needed to optimize public health programs, especially in areas with decreasing malaria prevalence. Therefore, we sought to explore the impact of malaria in pregnancy on fetal growth and newborn outcomes among a cohort of women enrolled in an IPTp-SP treatment program in a malaria-endemic region. The study was performed as a secondary analysis of a larger study to evaluate the impact of malaria exposure on neurodevelopmental outcomes (ClinicalTrials.gov NCT 00314899; unpublished data).

2. Materials and methods

From January 1, 2006, to December 31, 2009, the study team recruited pregnant women who attended prenatal care at Msambweni District Hospital, Msambweni, Coast Province, Kenya—a rural area where malaria is endemic [5]. Per Kenya Ministry of Health national policy, women received IPTp beginning in the second trimester, as well as iron, folic acid, and bed nets, as part of routine care. At the first prenatal care visit, consenting HIV-negative women were tested for peripheral malaria, demographic information was obtained, and a physical examination and an ultrasound examination were performed. Pregnant women with known medical disorders contributing to fetal growth restriction, placental dysfunction, twin pregnancy, and prematurity were excluded. Participating women who delivered a term, live infant at the Msambweni District Hospital had maternal venous, placental, and cord blood tested for hemoglobin level and malaria parasites. Neonatal anthropometric measurements were obtained within 24 hours of delivery, including birth weight, head circumference, and length. All women provided written informed consent. The study, which was part of a larger study on fetal immunity to malaria (unpublished), was approved by the institutional review boards at Kenya Medical Research Institute, Case Western Reserve University, and the University of North Carolina at Chapel Hill.

All anthropometric measurements were obtained by trained study staff. Maternal body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) was calculated based on maternal weight and height obtained at the first prenatal care visit. Low BMI was defined as lower than 18 pre-pregnancy by WHO and others. Because a pre-pregnancy BMI was unavailable, to explore the potential effects of undernutrition, BMI below the 10th percentile for gestational age at prenatal care was defined as low BMI. The 10th percentile BMI for the cohort ranged from 19.8 to 20.7 for the start of the second trimester to the start of the third trimester, respectively. Ponderal index (PI)—the ratio of infant weight to length, normalized to the third power—was also calculated, with PI below 2.32 defined as asymmetric growth.

Ultrasound examinations were performed using a SonoSite 180 Plus (SonoSite FujiFilm, Bothell, WA, USA) ultrasound machine by 2 radiology technicians who were trained in ultrasound procedures. All images and measurements were saved. Approximately 25% of randomly selected visits were reviewed on a monthly basis by the ultrasound expert who performed the training. Fetal biometry was performed according to standard techniques for determination of fetal gestational age and weight with standard software to calculate gestational age using the Hadlock formula [24]. Right and left uterine arteries were interrogated using standard techniques. Notching of uterine arteries was noted in

pregnancies greater than 25 weeks. Umbilical artery examination was performed on a free-flowing segment of umbilical cord.

The presence of malaria parasitemia was determined by polymerase chain reaction (PCR)/ligase detection reaction/fluorescent microsphere assay, as previously described [25]. For the purposes of the present study, analyses of malaria were restricted to *Plasmodium falciparum*: the species most commonly associated with adverse birth outcomes [2].

Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). Descriptive analyses were performed with χ^2 and *t* tests to evaluate differences in estimates. Linear and log binomial regression models were fitted to estimate risk ratios (RRs) and 95% confidence intervals (CIs) for estimated fetal and newborn anthropometrics, before and after adjusting for potential confounders. Based on previous studies, the potential modifying effects of maternal BMI and primigravida status were evaluated. $P<0.15$ for the interaction term was selected to indicate statistical significance. Additional potential confounders evaluated were sociodemographic status (household expenditures, education level, maternal age) and bed net use. A backward elimination strategy was used to fit the multivariate models for birth weight. Ultrasound measurements were stratified by 3-week gestational age groups (18–35 weeks) and compared malaria-infected women with uninfected women.

3. Results

Of the 813 women screened at prenatal care, 799 provided initial demographic information and were tested for malaria; 676 had an ultrasound examination at the first prenatal care visit at 18–35 weeks and were included in analyses of fetal measurements. Of these, 477 (70.6%) delivered a term, singleton, live infant in the study hospital.

Median gestational age at first prenatal care visit was 27 weeks (interquartile range [IQR], 24–31 weeks). Demographic characteristics and RR analyses are presented in Table 1 for women with and without *P. falciparum* infection at their first prenatal care visit. Overall, 87 (10.9%) women tested positive for *P. falciparum* malaria by PCR. In unadjusted analyses, women who were younger than 20 years of age (RR 2.10; 95% CI, 1.38–3.18) and primigravidas (RR 1.68; 95% CI, 1.11–2.54) had a higher risk of *P. falciparum* infection, while socioeconomic status (as measured by household expenditures), marital status, and educational status were not significantly associated with malaria. Women who were not using bed nets prior to prenatal care were more likely to be malaria positive (RR 1.71; 95% CI, 1.14–2.55). Women who did not have malaria treatment prior to prenatal care had a higher risk of being malaria positive (RR 1.68; 95% CI, 0.76–3.74). Women with moderate or severe anemia (hemoglobin <9 g/dL) had a higher risk of exposure to malaria. Median BMI was 24.6 (IQR, 22.2–26.9) and was similar among malaria-negative and -positive women. Only 4 of the women who were malaria positive had symptoms consistent with clinical malaria illness (data not shown).

Analyses adjusted for parity and stratified by gestational age to examine the association between concurrent *P. falciparum* status and fetal growth estimated by ultrasound are reported in Table 2. The mean estimated fetal weight measurements were generally lower for fetuses of *P. falciparum*-positive compared with *P. falciparum*-negative mothers;

however, except at 30–32 weeks of gestation, these differences were not significant at $P<0.05$. At 30–32 weeks, fetal weight, and head and abdominal circumference were significantly lower ($P<0.05$) for *P. falciparum*-positive mothers, while femur length measurements were similar between the groups across all gestational ages (data not shown).

Additionally, we examined measurements of uteroplacental blood flow for malaria-positive versus malaria-negative women. Umbilical artery resistance index (RI) was higher among *P. falciparum*-positive fetuses, with significantly different measurements ($P<0.05$) detected at ultrasound available at or prior to 26 weeks of gestation (Table 2). No significant differences in umbilical artery pulsatility index or systolic/diastolic (S/D) ratio were found; there were also no significant differences in uterine artery notching, RI, pulsatility index, or S/D ratio between the groups (data not shown).

Women whose births were included were comparable to women whose births were excluded (because of delivery outside the study hospital, voluntary discontinuance of study participation, loss to follow-up, premature delivery, or non-collection of samples and measurements) in terms of incidence of malaria, education level, gravidity, age, household expenditure, and maternal severe or moderate anemia. However, enrolled women who delivered a live infant in the study hospital were significantly less likely to have a low BMI percentile ($P<0.05$) compared with women whose birth data were not available.

Of the women with a live birth at the study hospital (n=480), 7.9% (n=38) were delivered by cesarean. Overall, 54.7% (n=263) of the neonates were male, and median gestational age was 39.0 weeks (IQR, 37.9–39.9)—neither of which differed by malaria status. In multivariate regression analyses, maternal factors that remained significantly associated (at $P<0.05$) with reduced birth weight were primigravidity, young maternal visit or at delivery were similar to those for newborns of women without *P. falciparum* in both adjusted and unadjusted analyses (Table 3). While the incidence of malaria at delivery was lower (8.8% [n=36]) than at prenatal care (10.9% [n=87]), women who were malaria positive at prenatal care were at higher risk of having any malaria (placenta, cord, or peripheral samples) at delivery (RR 2.1; 95% CI, 1.0–4.4).

Finally, we examined the role of maternal BMI (≤10th percentile, adjusted for gestational age) and malaria. Low BMI had a significant interaction ($P=0.06$) with *P. falciparum* status and, thus, an interaction term was included in the linear regression model to evaluate the association of malaria with birth weight. In the model for term births, adjusted for gravidity, malaria was not significantly associated with lower birth weights among women with normal BMI, but it was associated with decreased birth weight among women with low BMI (mean difference −370 g; 95% CI, −728 to −12; $P=0.04$) (Table 4). Gravidity did not have a significant interaction with malaria as defined a priori ($P>0.15$).

4. Discussion

Approximately 11% of women were positive for malaria at prenatal care and, similar to previous studies, risk of malaria was associated with primigravida status and younger maternal age [10]. We also found a significantly higher risk of malaria among women who did not use bed nets. In the region, distribution of free insecticide-treated bed nets, in

addition to the IPTp-SP program, was active during the study period and likely contributed to the relatively low burden of malaria infection compared with earlier studies in which 20%–40% of women were malaria positive at time of delivery [9,23].

There was a non-significant trend for reduced estimated fetal weight associated with malaria infection prior to 30 weeks, which the study was not powered to detect. At 30–32 weeks, there was a significant 123-g difference in estimated fetal weight, with no detectable difference after 32 weeks—consistent with previous research from the Democratic Republic of the Congo in which the highest rates of IUGR associated with malaria were at 28–33 weeks of gestation [8]. There was also a trend for higher umbilical artery RI among women with malaria, and the size of the difference was consistent with results from a recent study in which early malaria parasitemia was associated with increased umbilical artery RI among primigravid, but not multigravid, women [13]. While the differences in umbilical artery RI were not clinically significant (defined as 30% difference [26]), increased umbilical artery RI has been associated with IUGR [26]. Thus, the present results, together with previous studies, suggest that this may be an area for further research regarding the role of malaria and placental function on IUGR [15].

In the present population treated with IPTp-SP, malaria detected by PCR at prenatal care did not have a significant impact on birth weight or other anthropometric measurements. However, among women with the lowest BMI, malaria was significantly associated with reduced birth weight. While factors leading to low BMI are complex, low BMI appeared to be the maternal factor most highly associated with reduced birth weight in the present study. A previous study conducted in the Democratic Republic of the Congo found a similar trend, with significant impact of malaria primarily among those with indicators of undernutrition [8].

The widespread distribution of bed nets, even prior to enrollment, which was associated with decreased risk of malaria at prenatal care, probably contributed—together with the provision of IPTp-SP—to decreased risk for repeat or severe malaria infection, consistent with previous studies [9]. This confirms the important role of treatment programs in reducing the prevalence of malaria in pregnancy.

A limitation of the present study was that the women who were seen at prenatal care but subsequently delivered outside the study hospital or who did not deliver a live, term infant were excluded. Although the excluded women had higher rates of low BMI, they had comparable malaria rates to those with birth outcomes included. However, because malaria may also impact fetal outcomes through preterm birth, the study may underrepresent the potential impact of malaria in pregnancy [1]. Another consideration is that we evaluated malaria detected by PCR, rather than women with febrile illness or repeated malarial infections during pregnancy, so the findings are limited to the impact of potential modest malaria exposure on birth outcomes. However, even among women who received among the best care and had optimal outcomes, malaria and undernutrition were found to be associated with reduced birth weight.

Risk of malaria at delivery was associated with presence of malaria at first prenatal care visit, which was reduced among those using bed nets. We found that malaria detected by PCR at prenatal care was associated with only a modest reduction in fetal growth that, with IPTp and by term birth, no difference in birth weights was found. This suggests that, with good preventive care, the impact of exposure to malaria on fetal and newborn growth may be minimized. However, maternal BMI was highly associated with birth weight, and among women with the lowest BMI the impact of malaria was more pronounced. Additional research and programs to improve maternal nutritional health may be important to help further improve birth outcomes in low-resource settings, especially in areas where malaria prevalence is falling. The present results suggest that, among women given IPTp-SP and who delivered at a study hospital, mild malaria infection detected at first prenatal care visit was not associated with significant adverse outcomes.

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Synopsis

In Kenya, malaria in pregnancy was associated with transient differences in utero, and reduced birth weight was restricted to those with low body mass index.

Table 1

Maternal characteristics and risk for *Plasmodium falciparum* malaria at first prenatal care visit, 2006–2009[a]

Characteristic	Total[b]	*P. falciparum*	Unadjusted risk ratio (95% confidence interval)
Maternal age, y			
20–45	658 (82.3)	60 (9.1)	1.0
<20	141 (17.7)	27 (19.2)	2.10 (1.38–3.18)
Formal education			
None	163 (20.6)	17 (10.4)	1.0
Primary	526 (66.4)	58 (11.0)	1.05 (0.63–1,76)
Secondary/higher	103 (13.0)	11 (10.7)	1.11 (0.40–3.11)
Low household income			
No	299 (36.8)	27 (9.0)	1.0
Yes	514 (63.2)	60 (11.7)	1.31 (0.91–1.88)
Marital status			
Married/partner	698 (87.9)	72 (10.3)	1.0
Widowed/divorced/single	96 (12.1)	14 (14.6)	1.41 (0.83–2.40)
Gravidity			
Multigravida	601 (75.9)	56 (9.3)	1.0
Primigravida	191 (24.1)	30 (15.7)	1.68 (1.11–2.54)
Bed net use in last 3 months			
Yes	583 (73.6)	54 (9.3)	1.0
No	209 (26.4)	33 (15.8)	1.71 (1.14–2.55)
Malaria treatment in last 3 months			
Yes	88 (11.1)	6 (6.9)	1.0
No	706 (88.9)	81 (11.5)	1.68 (0.76–3.74)
Maternal anemia			
Hemoglobin ≥9 g/dL	506 (73.3)	38 (7.5)	1.0
Hemoglobin <9 g/dL	184 (26.7)	21 (11.4)	1.38 (0.95–1.99)
Body mass index[c]	24.2 (22.2–26.9)	23.9 (22.1–26.0)	—

[a] Values are given as number (percentage) or median (interquartile range) unless otherwise indicated.

[b] Differences in numbers are due to missing data.

[c] Calculated as weight in kilograms divided by the square of height in meters.

Table 2

Estimated fetal weight and umbilical resistance index stratified by gestational age and concurrent *Plasmodium falciparum* malaria at prenatal care visit, 2006–2009

Gestational age at measurement, wk	Concurrent malaria[b]	Estimated fetal weight[a]			Umbilical resistance index		
		Mean, g[c]	Mean difference (95% confidence interval)[c]	*P* value	Mean, g[c]	Mean difference (95% confidence interval)[c]	*P* value
18–20							
	Present (n=6)	279	−36 (−86 to 15)	0.16	0.82	0.042 (0.0098–0.74)	0.01
	Absent (n=45)	314			0.78		
21–23							
	Present (n=8)	542	16 (−43 to 77)	0.58	0.78	0.025 (−0.044 to 0.093)	0.5
	Absent (n=85)	514			0.75		
24–26							
	Present (n=16)	786	−22 (−84 to 38)	0.46	0.75	0.031 (−0.0016 to 0.064)	0.06
	Absent (n=118)	832			0.72		
27–29							
	Present (n=25)	1188	−31 (−94 to 33)	0.30	0.70	0.012 (−0.017 to 0.042)	0.4
	Absent (n=160)	1220			0.69		
30–32							
	Present (n=12)	1683	−123 (−235 to – 12)	0.03	0.67	0.015 (−0.022 to 0.053)	0.4
	Absent (n=121)	1808			0.66		
33–35							
	Present (n=7)	2334	−13 (−171 to 144)	0.87	0.68	0.029 (−0.022 to 0.081)	0.4
	Absent (n=73)	2356			0.66		

[a] Hadlock formula for estimation of fetal weight [25].

[b] *P. falciparum* malaria at prenatal care.

[c] Estimated mean and mean differences, adjusted for primigravida status.

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Table 3

Birth outcomes and malaria at delivery by *Plasmodium falciparum* malaria at prenatal care, 2006–2009[a]

	Malaria status[b]	Mean or No.	Adjusted mean[c]	Mean difference or adjusted relative risk (95% confidence interval)[c,d]	*P* value
Gestational age, wk					
	Positive (n=43)	38.8 ± 1.8	38.8	−0.6 (−1.2 to 0.9)	0.8
	Negative (n=388)	38.9 ± 3.2	38.9		
Birth weight, g					
	Positive (n=43)	3027 ± 368	3072	−5 (−131 to 121)	0.9
	Negative (n=422)	3039 ± 408	3077		
Infant length, cm					
	Positive (n=43)	48.9 ± 1.8	49.0	0.2 (−0.9 to 1.2)	0.7
	Negative (n=417)	48.8 ± 3.7	48.8		
Head circumference, cm					
	Positive (n=43)	34.4 ± 1.8	34.5	0.05 (−0.7 to 0.8)	0.9
	Negative (n=417)	34.3 ± 2.6	34.4		
Ponderal index <2.32 kg/cm^3					
	Positive (n=43)	7 (16.3)		0.96 (0.47–1.95)	0.9
	Negative (n=422)	69 (16.4)		1.0	
Cord hemoglobin <12.5 g/dL					
	Positive (n=42)	8 (19.5)		1.15 (0.57–2.21)	0.7
	Negative (n=365)	62 (17.0)		1.0	
Malaria at delivery[e]					
	Positive (n=42)	7 (16.7)		2.1 (1.0–4.4)	0.05
	Negative (n=365)	29 (7.9)		1.0	

[a] Values are given as mean ± SD or number (percentage) unless otherwise indicated.

[b] *P. falciparum* malaria at prenatal care visit.

[c] Mean and mean difference from linear regression model, adjusted for primigravida status.

[d] Risk ratio and 95% confidence interval from log binomial risk model, adjusted for primigravida status.

[e] *P. falciparum* malaria at delivery defined as cord, placenta, or peripheral, determined by polymerase chain reaction.

Table 4

Associations between birth anthropometrics and maternal malaria, stratified by maternal BMI, 2006–2009

	Malaria status[a]	Adjusted mean[b]	Mean difference (95% confidence interval)[b]	*P* value
Birth weight, g				
BMI ≤10th percentile	Positive (n=8)	2791	−370 (−728 to −12)	0.04
	Negative (n=26)	3081		
BMI >10th percentile	Positive (n=47)	3161	75 (−91 to 241)	0.4
	Negative (n=265)	3087		
Birth length, cm				
BMI ≤10th percentile	Positive (n=8)	48.1	−1.3 (−3.6 to 2.4)	0.4
	Negative (n=26)	49.0		
BMI >10th percentile	Positive (n=47)	49.1	0.7 (−0.9 to 1.4)	0.4
	Negative (n=265)	48.8		
Head circumference, cm				
BMI ≤10th percentile	Positive (n=8)	33.7	−0.8 (−3.1 to 1.5)	0.4
	Negative (n=26)	34.5		
BMI >10th percentile	Positive (n=47)	34.7	0.2 (−0.9 to 1.1)	0.8
	Negative (n=265)	34.5		

[a] *Plasmodium falciparum* malaria at first prenatal care visit.

[b] Adjusted for primigravida status.