Malaria during pregnancy in Rwanda

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CHAPTER 5

Fetal and Maternal Hemodynamics in Acute Malaria during Pregnancy

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Abstract

Objective: To measure maternal and fetal hemodynamics during acute malaria in pregnancy.

Methods: Time courses of maternal heart rate (MHR), maternal blood pressure (BP), and fetal heart rate (FHR) were performed until 56 days after initiation of anti-malarial treatment with artemether–lumefantrine. Women with malaria were hospitalized for at least 3 days until recovery.

Results: Mean baseline characteristics of pregnant women with malaria (n=38) versus pregnant women without malaria (n=39) were as follows: gestational age (28.8 vs 24.6 weeks; P=0.006); maximum FHR (165.3 vs 158.3 beats per minute [bpm]; P=0.054); minimum FHR (137.6 vs 128.7 bpm; P=0.016); mean BP (74.7 vs 80.9 mm Hg; P=0.001); pulse pressure (40.3 vs 42.1 mm Hg; P=0.300); and MHR (107.4 vs 81.3 bpm; Pb0.001). The geometric mean parasite count was 13 795 per µL. Complete time courses were collected from a subgroup of participants. For women with malaria, maternal body temperature and BP normalized within 24 hours and after 72 hours, respectively. The MHR among pregnant women without malaria showed a physiologic increase during pregnancy of approximately 7 bpm between days 0 and 56. The mean FHR among women with malaria normalized after 72 hours.

Conclusion: Acute malaria induces maternal and fetal hemodynamic changes.
Introduction

Malaria in pregnancy (MiP) causes over 10 000 maternal deaths worldwide each year [1]. The deleterious effects of MiP are different for chronic and acute malaria. In high transmission areas, chronic infection is the leading cause of anemia during pregnancy, low birth weight, fetal anemia, and fetal death [1,2]. In low-transmission areas such as Rwanda, MiP presents as an acute febrile disease [3]. Physiologic hemodynamic changes associated with pregnancy include increased cardiac output, heart rate, and stroke volume [4,5]. These reversible adaptations are most pronounced in the first and second trimesters, subsiding after delivery. The maternal heart rate (MHR) increases after 2–5 weeks of pregnancy and stabilizes in the third trimester at approximately 15–20 beats per minute (bpm) higher than the rate observed among non-pregnant women. These changes are compatible with decreased vascular resistance, probably triggered by hormonal changes. Blood pressure (BP) drops as utero-placental circulation expands and stabilizes by the third trimester. Increased blood volume is not matched by increased erythropoiesis, which leads to anemia. The acute effects of MiP include hemodynamic changes and spiking fever, which threaten fetal survival and induce premature labor. Acute malaria affects the microcirculation of vital organs; this effect can extend to the placenta during pregnancy [5]. Placental malaria is associated with increased BP before delivery in primigravidae but not in multigravidae [6]. Whether acute MiP also increases BP is not known. The MHR typically increases during acute malaria, parallel to increased body temperature and other signs of acute disease, and infected red blood cells undergo hemolysis, which contributes to anemia in pregnancy [5,7,8]. Data on fetal wellbeing, fetal circulation, and recovery time after a period of acute stress such as exposure to MiP are limited [9]. A need exists to further study maternal and fetal hemodynamics during acute MiP in regions like Rwanda where changing endemicity alters the presentation of MiP from chronic infection to acute disease. The aim of the present study was, therefore, to evaluate maternal and fetal hemodynamic parameters among pregnant Rwandan women with and without acute malaria.
Materials and methods

A prospective cohort study was conducted to compare maternal and fetal hemodynamic characteristics among pregnant women who (AL) and pregnant women without malaria. The present study was conducted at Rwamagana District Hospital and Health Centre located in the Eastern Province, Rwanda, between November 1, 2007, and February 30, 2010. The intensity of malaria transmission in this province is variable, hypoendemic, and subject to seasonal fluctuations. The study protocol was approved by the Rwandan National Ethics Committee; all participants gave written informed consent. Inclusion criteria for pregnant women with malaria were gestational age (GA) exceeding 12 weeks (late gestation was not an exclusion criterion); age older than 18 years; symptomatic and microscopically confirmed malaria; and willingness to provide written informed consent. The GA was estimated from the last menstrual period and/or by ultrasound measurement. Exclusion criteria were nonviable fetus; living outside the catchment area; and probable non-compliance with study protocols. Pregnant women without malaria and without history of treatment with AL in the current pregnancy who attended the prenatal care clinics of Rwamagana Health Center were invited to participate as a comparison group. These women were matched by GA and gravidity to the pregnant women with malaria. After enrollment, women with malaria were admitted to the hospital for 3 days and thereafter followed on an outpatient basis. To confirm malaria and identify the species, thick blood smears were examined by an experienced microscopy technician. For women in the comparison group, malaria was excluded by microscopy after which the baseline measurements were conducted. Patients with malaria were treated with 6 doses of AL. Each dose comprised 4 tablets (20 mg of artemether and 120 mg of lumefantrine per tablet), administered under supervision by a study nurse or physician. The time of the first dose was recorded as t=0 (day 0); consecutive doses were given at 8, 24, 36, 48, and 60 hours. Microscopic evaluation of thick blood smears was repeated every 4 hours within the first 24 hours of treatment and every 8 hours thereafter, until at least 72 hours after initiation of therapy or when parasite clearance was confirmed. Patients with malaria were clinically examined every 8 hours after enrollment, for 3 consecutive days. Fetal viability, GA, biometry, and fetal heart rate (FHR) were measured for all fetuses using portable ultrasonography conducted by a trained medical doctor. The first ultrasound examination was performed at t=0, prior to the first administration of AL. Cardiotocography (CTG) registrations were conducted every
4 hours on the first day of AL treatment, and every 8 hours for another 2 days. Fever (>38 °C) was treated with paracetamol. Maternal vital signs, including BP, pulse rate, respiratory rate, and temperature were measured upon enrollment for both groups of women. Routine blood tests (full blood count and HIV testing) and urine tests (urinalysis for cytology) were also performed at enrollment. For women with malaria, the blood count was repeated on day 3. All women were followed-up on an outpatient basis on days 7, 14, 21, 28, 35, 42, 49, and 56. At each follow-up visit, BP, pulse rate, respiratory rate, and temperature were measured and CTG and/or ultrasonography performed. Participants were reimbursed 2000 Rwandan francs (approximately US $3.5) for each visit. Participants who missed a visit were called or visited by the study nurse to reschedule their appointments. Emergency medical care during the study period was managed according to local standards. Cardiotocography was recorded following standard procedures for 30 minutes using a portable BD4002 fetal monitor (Huntleigh, Cardiff, UK). Recordings were stored electronically; the minimum, maximum, and mean FHR values were recorded separately in the case report form. Printed hardcopies were visually inspected to determine the mean FHR from CTG tracing segments that covered at least 10 consecutive minutes. A normal FHR was considered to be 120–160 bpm. The mean FHR was considered pathologic if deviations less than 2 bpm or greater than 25 bpm were found during a 2-minute recording. An FHR less than 120 bpm or greater than 160 bpm for at least 2 consecutive minutes was considered an abnormal bradycardia or tachycardia, respectively. Abnormalities were managed according to local guidelines, including labor induction when deemed necessary. Statistical tests were performed using SPSS version 16 (IBM, Armonk, NY, USA). Continuous and numeric variables, age, and FHR were checked for normality. If not normally distributed, these values were either transformed or non-parametric statistics were used. Statistical evaluations for parasite count were based on log transformations. At baseline, associations between numeric variables were tested for the entire cohort using Pearson r correlation coefficients. The Spearman test was used for non-parametric data, maternal or fetal hemodynamics (heart rate, BP), temperature, and parasite count. To determine differences between woman with and without malaria, FHR, MHR, BP, and temperature were compared using the Student t test for parametric tests and Mann–Whitney tests for non-parametric tests. These data were presented graphically. Differences within and between the 2 groups over time were analyzed first by visual inspection of mean data plots and their 95% confidence intervals. Significant differences were confirmed using repeated
measurements analysis (generalized linear model). A P value below 0.05 was considered statistically significant.

**Results**

In total, 40 patients with acute malaria and 40 women without malaria were invited to participate in the present study. Malaria could not be microscopically confirmed for 1 patient; 1 patient with malaria was excluded owing to intrauterine fetal death; and 1 woman without malaria withdrew on day 1 of the study. The initial analysis was, therefore, performed on 38 women with malaria and 39 women without malaria (Table 5.1). Details of the follow-up analysis are provided in Table 5.2.
Table 5.1: Patient characteristics at enrollment. *

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pregnant women</th>
<th>Mean difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With malaria(n=38)</td>
<td></td>
<td>Without malaria(n=39)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>24.7(18.0-39.0)</td>
<td>-2.1(1.5-3.0)</td>
<td>0.0010^b</td>
</tr>
<tr>
<td>Body weight</td>
<td>57.5(55.3-59.7)</td>
<td>-2.6 to 4.3</td>
<td>0.200^c</td>
</tr>
<tr>
<td>US-estimated gestational age</td>
<td>28.8(26.6-30.9)</td>
<td>-7.2 to 1.3</td>
<td>0.0060^d</td>
</tr>
<tr>
<td>Trimester,2nd/3rd</td>
<td>12/26</td>
<td>26/13</td>
<td>0.004^e</td>
</tr>
<tr>
<td>Parity,primi/secundi/multi/unknown</td>
<td>16/8/11/3</td>
<td>19/8/10/2</td>
<td>0.800^f</td>
</tr>
<tr>
<td>Geometric mean parasite count, per µl</td>
<td>13795(7910-24058)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Mean axillary temperature,°C (range)</td>
<td>36.8(34.9-38.8)</td>
<td>-1.2 to 0.32</td>
<td>0.001^a</td>
</tr>
<tr>
<td>Maternal blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>151.4(145.7-157.2)</td>
<td>-56.4 to 15.6</td>
<td>0.001^a</td>
</tr>
<tr>
<td>Maximum</td>
<td>165.3(158.2-171.7)</td>
<td>-14.0 to 0.1</td>
<td>0.054^a</td>
</tr>
<tr>
<td>Minimum</td>
<td>137.6(131.0-144.1)</td>
<td>-16.0 to 1.8</td>
<td>0.016^a</td>
</tr>
<tr>
<td>Maternal heart rate, bpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>101.6(98.8-104.4)</td>
<td>3.5-11.7</td>
<td>0.001^a</td>
</tr>
<tr>
<td>Systolic</td>
<td>61.9(59.0-63.6)</td>
<td>1.9-9.3</td>
<td>0.004^b</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>40.3(37.9-42.6)</td>
<td>-1.42 to 5.0</td>
<td>0.300^b</td>
</tr>
<tr>
<td>Maternal heart rate, bpm</td>
<td>107.4(102.2-112.7)</td>
<td>-32.4 to 19.9</td>
<td>&lt;0.001^a</td>
</tr>
<tr>
<td>Hemoglobin value, mmol/L</td>
<td>9.5(8.5-10.5;n=10)^c</td>
<td>1.5(-0.1 to 3.1)</td>
<td>0.060^b</td>
</tr>
</tbody>
</table>

Abbreviations: bpm, beats per minute; CI, confidence interval; NA, not applicable; US, ultrasound ^ Values are given as number or mean (95 % CI) unless otherwise indicated. Student t test. ^ X^2 test. ^ hemoglobin was not always measured exactly at t<0, owing to logistic constraints, unless anemia was clinically suspected. Only values obtained at t<0, just before drug administration, are presented.
Of the patients with malaria, 2 women delivered on study day 2 (GA 37 weeks and 39 weeks, respectively); 1 delivered on study day 3 (GA 36 weeks); 1 delivered on study day 7 (GA 38 weeks); and 1 delivered between study days 3 and 7 (GA 30 weeks). No premature deliveries occurred in the comparison group during the entire follow-up period. As a consequence, 28 women with malaria and 29 women without malaria had a complete series of CTG recordings through to study day 56. Although the initial number was 38 women with and 39 without, a complete series was available only for 28 women with and 29 women without malaria. Patient characteristics at enrollment are shown in Table 5.1. No significant differences were detected between the 2 groups with respect to age, body weight, and parity. Despite matching to GA and gravidity, the mean ultrasound-estimated GA was significantly higher for the group with malaria than for the control group (28.8 weeks versus 24.6 weeks; P=0.006). All women with malaria were infected with a single species (Plasmodium falciparum), which cleared with a mean time of 25.6 hours (maximum clearance time 56.0 hours) after initiation of AL therapy. Parasite recurrence was experienced by 4 patients experienced parasite recurrence (1 patient at day 42 and 3 patients at day 56). All 4 patients were re-treated with AL and responded favorably. For patients with malaria, significant positive correlations were found at baseline between maternal body temperature and MHR (Pearson r=0.393; P=0.015); minimum FHR (Pearson r=0.522; P=0.001); maximum FHR (Pearson r=0.545, P=0.001); and mean FHR (Pearson r=0.602, Pb0.001). No correlations were detected between parasite count and any of the maternal or fetal hemodynamic parameters at baseline. The MHR was significantly higher among women with malaria than among women without malaria until study day 28 (Figure. 5.1; orange line). The MHR of patients with malaria stabilized at day 7 at a rate approximately 15 bpm higher than that of the comparison group and stayed at this level until day 56. The mean difference between days 7 and 56 was 2.2 bpm (95%CI, −3.1 to 7.6; P=0.400, paired Student t test). Although the MHR of the comparison group also increased over time, it remained consistently lower than that of the patients with malaria through day 28.

Even after controlling for the 4-week difference in GA between the 2 groups, it still took approximately 3 weeks for the MHR of patients with malaria to return to the normal range (Figure. 5.2). The mean difference in MHR on day 21 for patients with malaria patients compared with day 49 of the control group was 5.9 bpm (95% CI, 0.3–11.6; P=0.041, Student t test). No significant correlation was uncovered in the women with malaria between the hemoglobin values at enrollment or on day 3, or their differences, and the MHR on day 56 (Table 5.1). Creatinine and
urea values also showed no correlation with MHR. Table 5.1 shows that both systolic and diastolic BP in the malaria group were significantly lower for the first 72 hours following enrollment than in the control group (101.6/61.3 mm Hg versus 109.0/66.9 mmHg; P=0.001, Student t test). During the course of pregnancy, the pulse rate among women without malaria showed an increase that was within the physiologic range (Figure. 5.1). The mean difference between days 7 and 56 was much less for the patients with malaria at 7.3 bpm (95% CI, 2.3–11.7; P=0.005, paired Student t test).

**Table 5.2:** Follow-up of women with and without malaria

<table>
<thead>
<tr>
<th>Group</th>
<th>Enrollment</th>
<th>Baseline</th>
<th>1*</th>
<th>2*</th>
<th>3*</th>
<th>7</th>
<th>14</th>
<th>21</th>
<th>28</th>
<th>35</th>
<th>48</th>
<th>56</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women with malaria</td>
<td>40</td>
<td>38</td>
<td>38</td>
<td>36</td>
<td>35</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
<td>33</td>
</tr>
</tbody>
</table>

* Days spent in hospital for women with malaria.

* Malaria could not be confirmed (n=1); intrauterine fetal death (n=1).

* Gave birth on day 2(n=2)

* Gave birth on day 3(n=1)

* Gave birth on day 7(n=1)

* Gave birth between day 3 and day 7(n=1)

* Withdrew from the study (n=1)

*b Cardiotocography was conducted at all time-points but only 28/33 women with malaria and 29/39 women without malaria had complete measurements for analysis at day 56.

By day 7, the mean pulse pressure (the difference between systolic and diastolic BP) was comparable for the 2 groups (Figure. 5.2). The mean FHR values for the subset of participants with
a full series of repeated measurements until day 56 (28 patients with malaria and 29 women without malaria) are shown in Figure. 5.1. The mean GA of the 28 patients included in Figure. 5.2 was slightly higher than that of the whole group of 38 patients (30.2 weeks versus 28.8 weeks). The mean GA of the 28 control participants included in Figure. 5.1 was not different for the whole group of 39 control participants (24.8 weeks versus 24.6 weeks). Fig. 1 illustrates that the FHR of women with malaria returned to normal within 1 day, followed by a short period during which the FHR was lower than that of control group. After 1 week, the FHR was within the normal range. The range between highest and lowest observed FHR values during 30 minutes of CTG registration was comparable between the 2 groups.

Figure 5.1: Fetal and maternal heart rate over time
Legend: Maximum (red round markers), minimum (blue diamonds) and mean (green triangles) fetal heart, measured during 30 minutes CTG registrations, during and after treatment with artemether lumefantrine for P. falciparum malaria. The mean maternal heart rate is indicated by
the orange line (no markers). The error bars indicate the 95% confidence intervals of the mean. The gray bands indicate the 95% confidence intervals of the mean of the measurements in healthy pregnant women.

**Discussion**

The principal finding of the present study is that acute malaria during pregnancy induces changes in fetal and maternal circulatory indicators which normalize after the initiation of therapy with AL, albeit at a different pace. No significant differences in outcome were detected between the 2 groups. One premature delivery occurred at 30 weeks after initiation of AL but was not clearly caused by malaria or treatment. The prolonged tachycardia observed in women following an episode of acute malaria (MHR b90 bpm until day 56) was a key finding of the present study. The biologic explanation for this phenomenon is unclear. Anemia and hypovolemia [10] were not apparent causes but neither could be excluded because blood tests were not performed after study day 3. The combination of rapidly normalizing blood pressure.
Legend: Systolic (red square markers) and diastolic (round blue markers) blood pressure for pregnant women with *P. falciparum* malaria, during and after treatment with AL. The error bars indicate the 95% confidence intervals of the mean. The gray bands indicate the 95% confidence intervals of the mean of the measurements in healthy pregnant women. The estimates indicate a statistically significance between maternal heart rate of malaria patients and of control women and prolonged tachycardia may point to reduced circulating blood volume; for example, by dehydration, vomiting, reduced cardiac stroke volume, or reduced systemic vascular resistance.

As MHR shows a physiologic increase during pregnancy, the mismatch in GA between the pregnant women with malaria and those without malaria was adjusted for. Nevertheless, this adjustment did not alter the conclusion of the present study that MHR is raised for several weeks after malaria. Other studies that have examined blood pressure in MiP were performed in areas with high transmission intensity and often with a different study design [8,11]. Owing to declining malaria transmission rates in Rwanda, longstanding placental malaria has become rare. The epidemiologic difference may explain the difference between the rapid normalization of FHR and BP found in the present study and the effects of chronic and placental malaria found in high transmission areas. The increased FHR found in the present study is probably owing to body temperature, which normalized rapidly after starting treatment with AL, augmented by administration of paracetamol [12]. Malaria induces placental hypoperfusion, increased umbilical artery resistance, and decreased fetal cerebral artery resistance and thereby protects cerebral blood flow [8,13]. This redistribution of fetal flow may also affect FHR.

In the present study, increased FHR was associated with decreased maternal BP but not with MHR. The rapid normalization of FHR corresponds to previous findings of the cerebral and umbilical flow in malaria [8,14]. It supports the concept that acute malaria causes reversible placental insufficiency and a temporary and reversible decrease in fetal–placental exchange that is not long enough to cause a significant reduction of birth weight [9]. Although the effects of the hemodynamic changes are reversible, close monitoring of both mother and fetus during an acute episode of malaria is important and should include frequent monitoring of MHR.

In addition, if a mother presents for prenatal care with disturbed hemodynamic values, recent malaria history should be established to further guide treatment and medical care. In conclusion, acute MiP increases MHR, FHR, and maternal BP. Changes in fetal hemodynamics normalize
within 1 week; however, MHR remains elevated for several weeks. The pathogenesis of the observed fetal and maternal hemodynamic changes requires further study because such changes might provide additional explanations of fetal distress during MiP.

Acknowledgments

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References


