Malaria and Perinatal Mortality in Central Sudan

Taha El Tahir Taha and Ronald H. Gray

Hospital and community studies were conducted in Central Sudan during 1989 and 1990 to determine the association between maternal malaria and perinatal mortality. There were 197 cases of stillbirth and 812 controls in the hospital study. In the community study, 36 perinatal and 31 neonatal deaths were compared with 1,505 and 1,495 survivors of the early neonatal and entire neonatal periods, respectively. There was no overall association between perinatal mortality and malaria. However, the risk of stillbirth (particularly macerated stillbirth) was significantly increased among women who reported malaria attacks in the first and second trimesters of pregnancy (odds ratio (OR) = 1.4, 95% confidence interval (CI) 1.1–1.9). A reduced risk was associated with attacks in the third trimester (OR = 0.4, 95% CI 0.2–0.8), but this probably reflects a bias resulting from shorter gestation in cases of stillbirth. Increased risk of neonatal mortality was associated with maternal malaria (OR = 2.1, 95% CI 1.0–4.5). In areas where malaria is prevalent, it is recommended that malaria prevention by personal protection, prophylaxis, and treatment be initiated early in pregnancy. Am J Epidemiol 1993;138:563–8.

fetal death; infant mortality; malaria; pregnancy

The World Health Organization estimates that each year there are approximately 7 million perinatal deaths and 20 million low birth weight births in developing countries (1, 2). It is also estimated that malaria is the cause of 1–2 million deaths each year, particularly among young children in tropical Africa (3).

Perinatal mortality is largely determined by the birth weight and maturity of the child (4). Several studies from Africa found maternal malaria during pregnancy to be associated with low birth weight (5–7), and substantial increases in mean birth weight were reported after a malaria eradication program in the British Solomon Islands (8). Malaria could lead to low birth weight either by premature delivery or by impaired growth in utero (9) due to anemia (10), fever, or impaired placental function (11).

Despite the evidence that maternal malaria causes low birth weight, the association between malaria during pregnancy and perinatal mortality has not been consistent (5, 9). This report, which assesses the association between malaria and perinatal mortality, is part of a larger investigation of determinants of low birth weight and perinatal mortality in Central Sudan.

MATERIALS AND METHODS

Nested case-control and cohort studies were conducted in two hospitals and six community health centers in Central Sudan during 1989 and 1990. In the hospital study,
the cases were stillborns weighing more than 500 g, and the controls were liveborn infants of normal birth weight (≥2,500 g). Early neonatal deaths were not included in the hospital study because of difficulties in the follow-up of mothers after discharge. In the community study, perinatal death (stillbirth and death within the first week of life) was compared with survival in the early neonatal period, and neonatal death (death of a liveborn infant within the first 30 days of life) was compared with survival in the first month of life.

In both studies, midwives measured the birth weight immediately after delivery, and trained female study workers administered a structured questionnaire. The purpose of the interview was to ascertain the sociodemographic characteristics of the mother and her medical and obstetric history. The study workers also conducted follow-up visits in the community to monitor the survival of the child during the first month of life. In the hospital study, a physician examined all infants at delivery to check for congenital anomalies.

Maternal malaria during pregnancy was determined from a history of malaria as diagnosed by either a physician or other health worker and/or from the mother’s report of symptoms suggestive of malaria. The questions about malaria included the reported number of attacks, the timing of the attacks, use of antimalarial drugs for treatment or prophylaxis, use of antibiotics, and exposure to insecticides. To distinguish malaria from other illnesses, questions were asked specifically about respiratory, urinary, or genital tract infections, and a history of hypertension, diabetes, or vaginal bleeding during pregnancy was obtained.

In addition, for hospital births, malaria at time of delivery was diagnosed from laboratory parasitologic and histopathologic studies. Parasitologic examinations included smears from peripheral maternal, infant cord, and placental blood. The blood slides were collected by trained nurses and technicians, stained with Giemsa, and examined for parasite species and counts by trained technicians at the Sennar Malaria Training Center, Sennar, Sudan. All slides were reexamined by a second technician to confirm the diagnosis. For histopathologic study, a small section of the placenta was collected by the midwife, fixed in formalin, and examined for malaria-causing parasites and changes in pigment or tissue by a histopathologist at the Gezira University reference laboratory in Wad Medani, Sudan. The technicians and histopathologist were not aware of the pregnancy outcome. In the community study, information on malaria was only obtained by history.

Descriptive, bivariate, and multivariate statistical analyses were carried out to determine the association between malaria and perinatal mortality. For analysis, malaria attacks were stratified by trimester of pregnancy and by whether the mother reported a single episode or recurrent malaria. Crude and adjusted odds ratios were estimated, and multiple logistic regression performed with SAS version 5.18 (SAS Institute, Cary, NC) was used to control for potential confounders and to appraise interactions. The variables used in adjustment are given in the tables. The 95 percent confidence intervals and χ² test for linear trend in proportions (12) were also calculated where appropriate.

RESULTS

In the hospital study, there were 197 cases of stillbirth (72 macerated and 125 fresh) and 812 liveborn controls of normal birth weight. Samples for laboratory diagnosis of malaria were obtained from 76.6 percent of the hospital cases (151 of 197) and 76.4 percent of the hospital controls (620 of 812). In the community study, there were 36 perinatal deaths, 31 neonatal deaths, 1,505 survivors of the early neonatal period, and 1,495 survivors of the entire neonatal period.

Table 1 shows the distribution of malaria diagnosed by maternal history or by laboratory tests among cases and controls and the odds ratios for perinatal and neonatal death. In the hospital population, there was
Malaria and Perinatal Mortality in Sudan

TABLE 1. Prevalence of malaria and crude and adjusted odds ratios for perinatal and neonatal death: Hospital and community studies, Central Sudan, 1989–1990

<table>
<thead>
<tr>
<th>Study setting and malaria diagnostic criteria</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude OR*</th>
<th>95% CI*</th>
<th>Adjusted† OR</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stillbirth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of malaria:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>107</td>
<td>423</td>
<td>54.1</td>
<td>1.1</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>81</td>
<td>359</td>
<td>45.9</td>
<td>0.8–1.5</td>
<td>0.8–1.7</td>
<td></td>
</tr>
<tr>
<td>Parasitology and histopathology§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>53</td>
<td>185</td>
<td>29.8</td>
<td>1.3</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>98</td>
<td>435</td>
<td>70.2</td>
<td>0.9–1.8</td>
<td>0.7–1.7</td>
<td></td>
</tr>
<tr>
<td>Community perinatal death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of malaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17</td>
<td>688</td>
<td>46.0</td>
<td>1.1</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>19</td>
<td>807</td>
<td>54.0</td>
<td>0.5–2.1</td>
<td>0.6–2.2</td>
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<tr>
<td>Community neonatal death</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>History of malaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>662</td>
<td>45.6</td>
<td>2.2</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11</td>
<td>813</td>
<td>54.4</td>
<td>1.0–4.9</td>
<td>1.0–4.5</td>
<td></td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
† Odds ratio adjusted for hospital, delivery complications, birth defects, previous reproductive losses, birth-to-conception interval, maternal weight, place of last delivery, use of hematinics during pregnancy, other illnesses, pesticide exposure, and infant's sex.
§ Data were not available for nine cases (4.6%) and 30 controls (3.7%).
§ Parasites detected in maternal, infant cord, or placental blood, and/or, placental malarial changes found on histopathologic examination.

no significant association between stillbirth and malaria diagnosed either by maternal report or laboratory findings. Similarly, there was no significant association between reported malaria attacks and perinatal death in the community. However, the crude and adjusted odds ratios for reported malaria and neonatal mortality were significantly increased in the community study (adjusted odds ratio (OR) = 2.1, 95 percent confidence interval (CI) 1.0–4.5). When birth weight was included in the multivariate model for neonatal mortality, the odds ratio was reduced and no longer significant (OR = 1.7, 95 percent CI 0.8–3.8). The frequency of use of antimalarial drugs during pregnancy among cases and controls was comparable. Malaria prophylaxis was reported by 2.0 percent of cases and 1.6 percent of controls, and malaria treatment was reported by 46.2 percent of cases and 48.0 percent of controls with malaria.

There was no significant association between the reported number of malaria attacks and the risk of stillbirth in the hospital or perinatal and neonatal deaths in the community. The mothers interviewed in hospital provided information on the timing as well as the number of malaria attacks during pregnancy. Table 2 shows the odds ratios for stillbirth by trimester of pregnancy, after adjustment for the number of episodes of malaria. The risk of stillbirth was significantly increased among women who reported single or multiple episodes of malaria during the first and second trimesters of pregnancy and significantly reduced among women who reported malaria attacks in the third trimester. The association with malaria in the first and second trimesters was largely ob-

TABLE 2. Association between the timing of reported malaria attacks and stillbirth: Hospital study, Central Sudan, 1989–1990

<table>
<thead>
<tr>
<th>Trimester of malaria attack</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR*†</th>
<th>95% CI‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st and 2nd</td>
<td>93</td>
<td>298</td>
<td>1.4</td>
<td>1.1–1.9</td>
</tr>
<tr>
<td>3rd</td>
<td>12</td>
<td>124</td>
<td>0.4</td>
<td>0.2–0.8</td>
</tr>
<tr>
<td>No attack</td>
<td>81</td>
<td>359</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
† Mantel-Haenszel stratified odds ratio, weighted for single and multiple episodes of malaria.
served for macerated stillbirth (OR = 1.8, 95 percent CI 1.0—3.2) and was not observed for fresh stillbirth (OR = 1.3, 95 percent CI 0.8—2.0).

**DISCUSSION**

The results of this study show that, overall, a history of maternal malaria during pregnancy is not associated with stillbirth or perinatal death (table 1), a finding in agreement with previous reports from Africa (5, 9). The absence of an overall association may be misleading, since we observed that the risk of stillbirth was significantly increased when there was a history of first and second trimester malaria attacks, but was reduced when there was a history of third trimester attacks (table 2). Furthermore, malaria attacks in the first and second trimester of pregnancy were only associated with macerated stillbirth, in which fetal death occurred long before delivery, and this is consistent with adverse effects earlier in pregnancy. Other studies have shown that malaria during pregnancy increases the risk of low birth weight and prematurity, and the effect is greater when the infection is acquired early in pregnancy (5-7, 13, 14). Therefore, it is plausible that malaria early in pregnancy could increase the risk of stillbirth through adverse effects on fetal growth and maturity.

Maternal reports of the timing of malaria are likely to be unreliable, and this could lead to biased recall. We found that, compared with laboratory diagnoses at the time of delivery, maternal history of malaria during pregnancy had a sensitivity of 65.4 percent and a specificity of 44.8 percent, but that the specificity was much higher (92.4 percent) for reported attacks during the third trimester (15). It is difficult to ascertain the timing of malaria during early pregnancy by parasitologic/histopathologic (16, 17) or serologic tests (5, 18) conducted retrospectively at the time of delivery, so a maternal history of malaria remains the only feasible method. There was no difference in the frequency of laboratory studies performed for hospital cases and controls (76.6 percent and 76.4 percent, respectively), so a differential detection/suspicion bias is unlikely.

More than one third of the hospital stillbirths were macerated fetuses, and the association with malaria was mainly observed in this subgroup of stillborns. We cannot identify a recall bias that would differentially increase the frequency of reported malaria attacks early in pregnancy only among mothers of macerated stillborn infants. However, these results could occur if there was confounding due to confusion between malaria and febrile syphilis in early pregnancy, since syphilis can cause macerated stillbirth. Routine serologic screening for syphilis is not conducted among pregnant women in this setting, so we cannot exclude the possibility of confounding of syphilis, malaria, and macerated stillbirth. However, we think that such confounding is unlikely, for the following reasons. According to clinicians in the hospitals at Wad Medani and Sennar, syphilis and other sexually transmitted diseases are not common in this population. All live and stillborn infants were examined at birth, and no infants were reported to have the stigmata of congenital syphilis. No symptoms suggestive of primary or secondary syphilis were reported by mothers in response to questions regarding illness during pregnancy. Finally, although syphilis is classically associated with macerated stillbirth, there are other causes of fetal death with delayed expulsion that can lead to maceration. In summary, the lack of laboratory screening for syphilis and the lack of a confirmed history of malaria early in pregnancy are potential limitations of this study. Nevertheless, the finding of an increased risk of perinatal mortality associated with reported malaria early in pregnancy is consistent with other reports of the adverse effects of malaria on fetal development and maturity, and the possibility of a causal association cannot be excluded.

The decreased risk of stillbirth associated with malaria in the third trimester is likely to be an artifact due to shorter gestation
among stillborns as compared with liveborn controls, an effect described as "opportunity bias" (19). The median length of gestation was 36.0 weeks for stillbirth cases and 40.0 weeks for controls. Thus, the third trimester was truncated by 33.0 percent among cases relative to controls. We believe the failure to observe any overall association between stillbirth and malaria during pregnancy is due in part to the spurious reduced risk of third trimester infection offsetting the increased risk of infection earlier in pregnancy.

We found an increased risk of neonatal mortality associated with malaria during pregnancy (table 1). It is thought that maternal malaria contributes to neonatal mortality (3, 7), and that premature labor, placental insufficiency, low birth weight, and congenital malaria are possible mechanisms (9, 20). Several biologic, demographic, and social factors also contribute to neonatal mortality (21, 22), but birth weight is a major proximate determinant (23). Our analyses support the hypothesis that the effect of malaria on neonatal mortality is mediated via an effect on birth weight, since in the multiple logistic regression model, the malaria effect (OR = 2.1) is reduced and no longer statistically significant after adjustment for birth weight (OR = 1.7).

In conclusion, this study suggests that maternal malaria significantly increases the risk of stillbirth and neonatal mortality. However, the association between stillbirth and malaria is found only for infections during the first two trimesters, and failure to account for the timing of malaria during pregnancy may mask a significant effect. In areas where malaria is endemic, such as Central Sudan, efforts to prevent malaria by personal protection, prophylaxis, or treatment should be initiated early in pregnancy.

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REFERENCES