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Malaria and low Birth Weigh in Central Sudan*

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A nested case-control hospital study and a midwife-based community cohort study were conducted in central Sudan during 1989 and 1990 to assess the contribution of mesoendemic malaria to low birth weight. Malarial infection was determined by maternal history, parasitology, and histopathology. There were significant associations between a maternal history of malaria and low birth weight in the hospital study (adjusted odds ratio (OR)=1.6,95% confidence interval (CI)1.2-2.1) and the community study (OR=1.7,95%CI 1.3-2-3). Attributable risk percentages were high and were com- parable in the hospital study (22.2%) and the community study (24.5%) a significant trend of increased risk of low brith weight was observed with increasing number of report malaria attacks, with attacks occurring earlier in pregnancy, and with higher parasitemia. In addition, the risk of low birth weight associated with malaria was higher among primiparous women than among multiparous women. The mean birth weight of infants whose mothers had malaria during pregnancy was significantly lower than the mean birth weight of whose mothers did not. Malaria treatment, chemoprophy- laxis, and use of insectiones decreased the risk of low birth weight and are recom- mended as appropriate interventions. These measures should target primigravid women and should be initiated early in pregnancy. Am J Epidemiol 1993;138:318-25.

Infant, low weight; malaria; parasitology; pregnancy outcome

Malaria is the most common infectious disease in sub-saharan Africa, where there are around 90 million clinical cases and one million deaths annually (1,2). In the Sudan, a nation with an area of one million square miles (1.6 million square km) and a popu- lation of 24 million, malaria transmission is hypoendemic in the northern part of the country, mesoendemic in the central savan- nah areas, and holoendemic in the tropical and equatorial forests of the south (3). In recent years, malaria transmission has been influenced by recurrent drought, population movements, extension of agricultural irrigation projects, the spread of drug and insecticide resistance, and deterioration of the health infrastructure in many Africa countries (2). Several investigators have reported lower birth weights with placental malarial infection (4-8). However, these studies did not differentiate between preterm and full term low birth weight and did not take into account other determinants of low birth weight which may have confounded the association. In addition, most of the previous

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studies were conducted in areas where malaria was hyperendemic and treatment facilities were scare (9).

Malaria could influence birth weight by inducing preterm labor or by retarding intrauterine growth (10). Histologic and ultra structural studies have shown that plasmodium falciparum infection may result in substantial placental damage, and previous infection may cause pigment deposition and basement membrane thickening, which can impair placental function (11,12). Pregnancy is believed to reduce immunity to malaria and to increase susceptibility to sever clinical illness (4,13-15). In addition, malaria causes anemia (16), and this could affect birth weight by impairing oxygen transport to the fetus (17). Another common clinical feature of malaria is fever, which, if recurrent, could increase catabolism, limit caloric intake, and lead to decreased availability of energy to the fetus, with consequent impairment of fetal growth (17).

General Sudan is the site of several large agricultural projects and is the most economically developed region of the country. Traditionally, cotton was the main cash crop, but recently, wheat, sorghum, peanuts, and sugar cane have been extensively cultivated. Although these irrigation projects greatly influence the livelihood of the local communities they may promote endemic health problem such as malaria, schistosomiasis, and diarrheal diseases. The Blue Nile Health project was established in 1979 to combat these problems. The project has been effective in lowering the prevalence of these diseases in Gezira province through environmental management, provision of safe water, health education, and community participation (3).

The purpose of this paper was to assess the contribution of malaria to low birth weight and prematurity in the Gezira and Blue Nile provinces of Central Sudan. Malaria is mesoendemic and stable in the irrigated areas of Gezira province, and it is mesoendemic to hyperendemic and occasionally unstable in Blue Nile province (3).

Material and methods. Both a hospital-based study and a community-based study were conducted. The hospital investigation, which consisted of surveillance of all singleton births and a nested case control study, was conducted during the April 1989-july 1990 in Wad Medani Hospital, Gezira Province, and Sennar Hospital, Blue Nile Province. These hospital are the main health facilities in their respective regions and serve about tow million people. Acase was defined as aliveborn low birth weight infant (< 2,500g), while a control was defined as aliveborn infant with abirth weight of $\geq$ 2,500g. Two controls per case were selected from livborn infants succeeding each case birth. Controls were identified from the same hospital as cases,

and mothers of both cases and controls underwent similar diagnostic procedures and interviews. An effort was made to include all infants who fulfilled the case definition. There were 397 low birth weight infants born during the entire period of investigation, and 348(88.0 percent) were enrolled in the study. The main reason for failure to include a case was early unplanned discharge of the mother from the hospital due to social reasons or death of the newborn.

The community study was a midwife based surveillance study conducted in six health centers which provided routine outpatient and antenatal care for the periurban and rural populations between the cities of Wad Medani and Sennar. All midwife assisted singleton births between April 1989and March 1990 were identified and followed postnatally. Thirty-four village midwives and health visitors who attended home deliveries participated in the study and were supervised by a study worker in each center.

Collection of data and specimens. Interviews were conducted by trained study workers (women with a secondary school or college education) in the hospital and the community soon after delivery. In the hospital study, the interviewers were unaware of the case/control status of the mothers. Enrolment of cases and controls was conducted by a midwife at delivery, and the interviewers had no information on the birth weight of the child. In the community study, where every woman giving birth was interviewed, it was not possible to conceal the birth weight of the child from the study worker because she participated in verification of weight measurements.

Information was obtained retrospectively on maternal sociodemographic characteristics, obstetric history, and history of malaria or other illnesses during pregnancy, using a structured questionnaire. The questions and criteria for definition of each variable were the same in both studies. Interviews were pilot-tested in the two hospitals and four health centers prior to initiation of the study. A history of malaria included malaria diagnosed by a physician or other health worker and/or symptoms reported by the mother as those of malaria. Questions were also asked about the number of malaria attacks, timing of the attack (S) during pregnancy, use of malaria treatment and chemoprophylaxis, and use of insecticides. In the community study, however, no inquiry was made about the timing of malaria attacks or use of chemoprophylaxis. To further distinguish between malaria and other illnesses, workers asked questions about the mothers history of respiratory, urinary, genital tract, and bilharzial infections. The questions on other illnesses during pregnancy included questions on history of hypertension, diabetes mellitus, and vaginal bleeding.

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The study workers also conducted anthropometric measurements of each mother and child. Birth weight was measured immediately after birth by the attending midwife using a portable scale in the community and a standard scale in the hospital. Gestational age was determined from the date of the last menstrual period, and in the hospitals, gestational maturity of the newborn was assessed using physical and neurologic signs (18). Preterm low birth weight was defined as a gestational age of less than 37weeks and a birth weight of less than 2,500g, while full-term low birth weight was defined as a gestational age of $\geq$ 37 weeks and a birth weight of less than 2.500g.

In the hospital, in addition to maternal recall, laboratory parasitologic and histo-pathologic investigations were carried out to confirm malarial infection at delivery. Standard procedures were used to collect specimens (19.20). Parasitologic examinations were conducted on Giemsa-stained slides prepared from maternal, placental, or infant umbilical cord blood at the sennar Malaria Training Center (Sennar, Sudan).A team of trained technicians examined 100 microscopic fields on each slide to determine parasite species and counts. All slides were reviewed by a second technician to confirm the diagnosis. Histopathologic examination of placental sections was conducted by a histopathologist (A.A.M) at the Gezira University Reference Laboratory in Wad Medani. The morphologic changes observed were a combination of malarial pigment deposits, the presence of parasites in the intervillous spaces, concentration of macrophages in the intervillous spaces, an excess of perivillous fibrinoid deposits, and Iymphocytic infiltration (11,12,19). The technicians and the histopathologist did not know the outcome of any pregnancy. We attempted to assess the validity of the malaria history reported by mothers using the parasitology or histopathology diagnoses as a standard. The limitation of this approach is that the maternal histories reflect malaria that occurred at any time during pregnancy, whereas the laboratory tests could only detect malaria that existed at the time of delivery.

Analysis. Data analysis included descriptive, bivariate, and multivariate statistics. We estimated crude odds rations to assess the association between low birth weight and malaria. We used stratified or multiple logistic regression analyses (21) to adjust for potential confounding. We calculated the 95 percent confidence intervals for the crude and adjusted point estimates and used them as tests of statistical significance. Where appropriate, we also conducted the $\times^2$ test for linear trend in proportions (22). We estimated the population attributable risks in order to determine the contribution of malaria to low birth weight after adjustment for the effects potentially confounding factors, using the adjusted odds ratios and the proportions of cases in

each stratum of the risk factor (23).

Results

Hospital and community data. Table I shows the prevalence of reported malaria among mothers of cases and controls. The prevalence of malaria was higher among low birth weight cases than among controls, and there was a consistent significant increased risk of low birth weight associated with a maternal history of malaria after adjustment for the potential confounders listed in the first footnote of table. 1.the odds ratios were higher for preterm low birth weight than for full-term low birth weight. The population attributable risks were comparable between the hospital and community studies, and were around 35.5 percent for preterm low weight. There was a significant trend of increasing risk of low birth weight with increasing number of reported malaria attacks during pregnancy in the hospital and community populations, and this trend was most pronounced for preterm low birth weight (table 2). Since the number of episodes could have been confounded by the timing of malaria during pregnancy, we examined the association between low birth weight and trimester of first malaria attack among women with multiple malaria episodes in the hospital study, where data on timing of attacks were available (table3). The risk of low birth weight was highest for multiple episodes of malaria that occurred earlier in pregnancy ($\times^2$ for trend=9.9;p=0.00).

Mean birth weight was significantly lower among infants of mothers who reported having malaria during pregnancy than among infants of those who did not (table 4). The difference in mean birth weight was greater in the hospital study (219.2g) than in the community study (74.1g) Among women who reported having malaria in both the hospital and community studies, the mean birth weight among infants of primiparous women was significantly lower than among infants of mul-tiparous women (2,709.1g vs.2,876.4g in the hospital study, t=2.7,p=0.006; and 2,949.4 g vs.3.044.9 g in the community study, t=1.7,p=0.09) in addition, the risk of low birth weight was significantly decreased with malaria treatment (odds ratio (OR)=0.63,95 percent confidence interval (CI) 0.43-0.94). Malaria chemoprophylaxis and use of insecticides during pregnancy decreased the risk, but the results were not statistically significant.

Laboratory-based hospital data. Table 5 shows the prevalence of laboratory confirmed malaria at the time of delivery among cases and controls in the hospital population. The prevalence of confirmed malaria was consistently higher among low birth weight cases than among controls, and there was a significant association between low birth weight and confirmed malaria after we controlled for other risk factors.

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With laboratory-confirmed malaria at delivery used as the standard, the estimated sensitivity of reported malaria was 65.4 percent (95 percent CI 59.5-71.1), and the specificity was 44.8 percent (95 percent CI 40.8-48.9). However, the specificity was much higher for reported maternal malaria during the third trimester (92.4percent;95 percent CI 89.4-95.3)

The adjusted risk of low birth weight associated with laboratory confirmed malaria was higher among primiparous women (OR=2.2,95 percent CI 1.3-3.5)than among multiparous women (OR =1.3,95percent CI 0.9-1.9). in addition, there was evidence of an increasing risk of low birth weight with higher paracitemia at the time of delivery among primiparous women; the odds ratio for low birth was 2.6 (95 percent CI 1.1-6.2) for parasite counts of 1-1,000 per 300 white blood cells and 3.3 (95 percent CI 1.0-11.6) for counts of > 1,000 parasites. This trend was highly significant ($\times^2$ =10.0,p=0.002). Among multiparous women, on the other hand, the trend was not significant ($\times^2$ =3.3,p=0.07).the mean birth weight of infants whose mothers had confirmed malaria was 2,785.8 g, compared with a mean birth weight of 2,960.5 g for infants of mothers without confirmed malaria. The difference of 174.7 g was statistically significant (t=3.3,p< 0.001).

Discussion. This study showed a clear association between low birth weight and maternal malarial infection during pregnancy. The consistency of the association between the hospital study and the community study after adjustment for potential confounders (tables 1 and 5), the increase in risk with increasing number of reported malaria at-tacks (table2) or higher parasite counts, the decrease in risk with potential intervention measures, the effects on mean birth weight (table 3), the biologic, plasuidibility, and the consistency of these findings with previous reports (2,4,7,14,15) all support a causal explanation for the association between maternal malarial infection during pregnancy and low birth weight in the offspring. Although both preterm and full-term low birth weight were associated with malaria, in general the risks were higher for preterm low birth weight. The estimation of gestational age is difficult and is subject to misclassification. But we have no reason to believe that there was differential bias affecting the association between prematurity and malaria. Moreover, such misclassification would not affect the overall risk of low birth weight.

The adjusted population attributable risks were high (table1), indicating that malaria is an important contributor to low birth weight in central Sudan. Unlike earlier studies, which were conducted in hyperendemic or holoendemic areas of Africa with stable transmission, the current study pertains to an area where malaria transmission is low to moderate (mesoendemic) and unstable, depending on environmental factors

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such as irrigation and rainfall in the Gezira and Blue Nile areas(3). This emphasizes the importance of malaria under all patterns of endemicity.

Our findings with respect to the timing of malaria attacks during pregnancy have considerable relevance to prevention. The risk of low birth weight was highest in the first and second trimesters (table3),which suggests that the insult to the fetus occurs early in pregnancy and that efforts to improve the birth weight of the child should start in the first trimester. This is challenging in developing countries, because women in these countries usually seek antenatal care late in pregnancy. Other studies have shown an impact of chemoprophylaxis, but frequently prevention is initiated late in pregnancy (2). In addition, infants of primiparous women were at particularly high risk of low birth weight, which suggests that special efforts should be focused on this group. The marked effect of malaria in primiparous women is thought to be due to "of host immunity by the parasite (9) or the result of depressed maternal immunity during the first pregnancy (2, 14,20).

The validity of the diagnosis of malaria based on maternal history is a concern in this study, particularly because of the possibility of differential recall bias. however, we do not believe that the associations between maternal malaria and a increased risk of low birth weight were due to a reporting bias, because the adjusted odds ratio of 1.6, based on a maternal history of malaria, was the same as the odds ratio estimated from laboratory diagnoses (tables 1 and 5). In addition, the proportions of cases and controls with laboratory investigation of malaria were similar (79.6 and 76.4 percent, respectively). It is important to note that retrospective identification of malarial infection is difficult because parasitology, histopathology, and serology detect only current or recent infections (12,19,20). When the maternal reports of malaria were validated against the laboratory diagnoses at the time of delivery, estimates of the sensitivity and specificity of the malaria history were modest. However, the laboratory diagnoses rep-recent imperfect standards; parasitemia only reflects current infection at the time of blood sampling, and a negative smear may result from recent therapy or from the episodic nature of the parasitemia. In addition, placental histopathology may indicate current or recent infection, but morphologic changes cannot be used to estimate the timing of past malaria attacks. Thus, reported malaria history which represents the mothers cumulative experience throughout pregnancy, provides the only measure for retrospective estimation of malaria attacks occurring early in gestation. There are multiple risk factors for low birth weight, but it is unlikely that our findings were due to confounding, since adjustment for the risk factors listed in table I had minimal effects on the estimated odds ratios.

In conclusion, this study suggests that malaria contributes significantly to low

birth weight irrespective of the prevailing levels of endemicity. Programs for protection against malaria should target primarily pregnant women, particularly primigravid women. Malaria treatment, chemoprophylaxis, and measures taken to eliminate malaria vectors are appropriate methods, but they must be initiated early in pregnancy.

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