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Epidemiology of Malaria in Pregnancy in Central India

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Analysis of three years of data from a malaria clinic operated by the Indian Council of Medical Research (ICMR) in the Government Medical College Hospital in Jabalpur, central India, showed a high malaria prevalence among pregnant women, which was statistically highly significant (P <0.0001) compared with the situation among non-pregnant women. Cerebral malaria was a common complication of severe *Plasmodium falciparum* infection, with a high mortality during pregnancy, requiring immediate attention. The study also showed that malaria infection was more frequent in primigravidae, falling progressively with increasing parity. Mean parasite densities were significantly higher in pregnant women compared with non-pregnant women for both *P. falciparum (P <0.001;* df=137) and *P. vivax (P*<0.05; df=72) infection. Pregnant women with falciparum or vivax malaria were significantly more anaemic than non-infected pregnant women or infected non-pregnant women.

The average weight of 155 neonates from infected mothers was 350 g less than that of 175 neonates from non-infected mothers. This difference in birth weight was statistically significant for, both *P. falciparum (P <0.0001;* df = 278) and *P. vivax (P<0.0001; df* = 223) infection. Congenital malaria was not recorded. We conclude that pregnant women from this geographical area require systematic intervention owing to their high susceptibility to malaria during pregnancy and the puerperium.

Introduction

It is generally agreed that the prevalence of malaria is higher among pregnant women than other groups (1), and that this can lead to abortion, intrauterine fetal death, premature delivery and even maternal death (2). The greater part of our knowledge about malaria in pregnancy is derived from studies carried out in tropical Africa, which show differences in the clinical epidemiological pattern of malaria in pregnancy from one endemic setting to another (3). Systematic studies from malaria-endemic regions in India are lacking except for those carried out in Chandigarh (4) (5) and Surat, Gujarat (6), two areas that differ in climate, intensity of malaria transmission, use of malaria

control measures, and socio-cultural attitudes towards the disease. In the absence of such a study in central India, we examined the relationship between malaria infection and pregnancy in jabalpur - information which would help to develop control strategies. This endemic region is of special interest because the population is exposed to malaria from both *Plasmodium vivax and P.falciparum.*

Materials and methods Study area

Jabalpur district (area, 10,160 km^2) in central India (Madhya Pradesh), has a mixed rural, tribal, and urban population (total, ca. 2.2 million). The district is mostly rocky with an undulating terrain and has no proper drainage and irrigation facilities. The study was carried out in the Government Medical College, which is surrounded by typical urban slums; the river Narmada, about 5 km away, supports the breeding of three primary vector species - Anopheles culicifacies, A.fluviatilis and A.stephensi.The Medical College is the largest medical facility in the district and serves as both a hospital for local people and a referral hospital for the adjoining six districts. Both *P. vivax and P. falciparum* malaria are common in the area (7), and there is a definite seasonal trend (8). Cases are mainly due to *P. vivax* in the dry hot season (March-June) and to *P. falciparum* during the monsoon and post-monsoon period. Resistance of *P. falciparum to* chloroquine is common (9) (10).

Antenatal clinic

The obstetrics and gynaecology department of the Medical College has a busy antenatal clinic, which an average of 500 women attend every month. Pregnant women usually first attend the antenatal clinic in the fourth or fifth month of gestation and make three or four visits before delivery. At enrolment, a clinical and obstetric history is recorded for each woman by the medical officer, followed by a full examination, including measuring the woman's weight, temperature, pulse, blood pressure, fundal height, fetal heart rate, and determining the presence of oedema or anaemia. An estimate of gestational age is also recorded, based on the fundal height and fetal size. The majority of women attend the antenatal clinic for a routine check-up, but those with fever or a history of fever at some time during the pregnancy are referred to the malaria clinic in the Malaria Research Centre (Indian Council of Medical Research). Fever cases among those attending other departments in the hospital with minor complaints, or while visiting patients or accompanying patients to the hospital, are also referred to the malaria clinic.

There were over 4000 deliveries in 1992 at the Medical College and the number has been increasing steadily. Women attending the antenatal clinic are given one month's supply of iron (II) sulfate tablets (60 mg daily) and folic acid tablets (5 mg daily). Deliveries, are usually conducted by nurses and the birth weights are recorded within 24 hours by one of the clinic staff. Over 85% of the obstetric admissions to the hospital lived within a few miles of the hospital; about 5% were women from surrounding villages who arrived only when labour was imminent, and about 10% were referred from nearby districts.

Study Population

The study was carried out in 1992-95 on women with fever or a history of fever, including pregnant women from 12 weeks gestation up to 40 days after delivery. All the women belonged to the lower socio-economic groups and worked in their homes and fields until term. Personal and reproductive histories were obtained from all the study subjects, and they were asked about any treatment taken for malaria during the pregnancy. Their answers were not always clear, many women being unaware of the names or nature of the drugs they had received. Thick and thin films of finger-prick blood collected from the women were stained with Giemsa and examined under the microscope. On first presentation each case was classified as new and on subsequent presentations as old, and their parasitic findings were recorded separately. Only the first parasitic (febrile) episode of malaria was considered for data analysis and parasite counting. All 40 cases referred from neighbouring districts were excluded from the study because their personal and reproductive records were not complete; they often reported at a late stage in a critical condition, and the majority of these women died within 96 hours of admission to hospital.(11)

There were two control groups in the study. The first group, chosen for assessment of the prevalence of vivax/falciparum malaria and parasite density, consisted of non-pregnant women of reproductive age suffering from malaria who were attending the hospital or malaria clinic for minor complaints during the same period. The second group, chosen to compare anaemia and low birth weight, were pregnant women from the study group who had fever but no malaria infection. These controls were matched with infected pregnant women for parity, since few women knew their ages. Thick blood smears were examined for parasite counts (per mm^3) using standard methods.(12) The women were treated with chloroquine (1500 mg in divided doses), as recommended by the national malaria eradication programme.

The results of routine laboratory investigations (complete haemogram, blood groups, etc.) were taken from the hospital records. Haemoglobin was determined using the

cynanomethaemoglobin method; a haemoglobin level <10 g/dl was considered low. The birth weights of neonates were also obtained from the hospital records; low birth weight was defined as <2.5 kg. The presence of placental infection and cord blood analyses could not be included in the present study because these investigations were not carried out in the hospital.

Blood smears were prepared from all neonates (with and without fever) whose mothers were enrolled in the study. All neonates for the study of low birth weight were full-term deliveries (twins excluded).

The results were analysed according to the type of malaria infection, parasite density in peripheral blood, parity, and period of gestation. Differences in means were tested by student's t-test and differences in proportions by the Z-test. The study was approved by the Ethical Committee of the Malaria Research Centre.

Results

Table 1 shows that of 2127 pregnant women, 121 were infected with *P.vivax* (33%) and 244 with *P. falciparum* (67%), of whom 17 were cerebral malaria cases. Among 1984 non-pregnant women with fever, there were only 115 falciparum and 35 vivax malaria cases. The slide positivity rate (SPR) and slide falciparum rate (SFR) were significantly higher (*P* <0.001) in pregnant than non-pregnant women.

Table 1: Malaria Parasitaema, Anaemia during Pregnancy, and Low Birth Weight Among the Study Subjects in Central India.

	All Cases[a]	Cases with P.Vivax infection	Cases with P.falciparum infection	Controls 1[a]	Controls 2[a]
No. tested	2127	365	365	1 984	
No. Selected	365 (17%)	121 (33%)	244 (67%)	150 (8%)	1 762
					(i.e 2127-365)
Pregnant	Yes	Yes	Yes	No	Yes
Fever	Yes	Yes	Yes	Yes	Yes

Malaria	Yes	Yes	Yes	Yes	No
No. with Hb data available	271(74%)	83(69%)	188(77%)	85(57%)	88(5%)
Mean Hb +/- SD (g/di)	_	9.05 +/- 1.39	6.42 +/- 1.98	9.68 +/- 1.43	10.03 +/- 1.11
No. with birth weight available	155(42%)	50(41%)	105(43%)	-	175(10%)
Mean wt +/- SD (Kg)	2.18 +/- 0.25	2.22 +/- 0.30	2.15 +/- 0.21	_	2.53 +/- 0.43

A Cases are Pregnant women with fever

Controls 1 = infected non-pregnant women.

Controls 2 = noninfected pregnant women

Table 2 shows the distribution of malaria cases by trimester and parity; 121 (23%) of 527 women in their first pregnancy (Po) were parasitaemic, compared with 184/1075 (17%) in their second and third pregnancies (P_{1-2}) and 60/525 (11 %) in their fourth (or more) pregnancy. Overall, the mean prevalence of vivax malaria was highest during the second trimester (10%) and lowest during the puerperium (2.5%). However, the mean prevalence of falciparum malaria was nearly the same in all trimesters and the puerperium.

Table 2: Malaria Parasitaemia by Parity and Stage of Pregnancy

	Stage of Pregnancy									**Pueperium**			**Total**		
	1st trimster			**2nd trimester**			**3rd trimster**								
	Cases	**PVa**	**PFb**	**Cases**	**PVa**	**PFb**	**Cases**	**PVa**	**PFb**	**Cases**	**PVa**	**PFb**	**Cases**	**PVa**	**PFb**

Parity															
P_0	39	6	7	132	16	20	317	16	42	39	1	13	527	39	82
P_{1-2}	50	3	5	168	20	17	505	32	59	352	9	39	1075	64	120
P_{3+}	35	2	4	77	2	10	275	11	15	138	3	13	525	18	42
Total	124	11	16	377	38	47	1097	59	116	529	13	65	2127	121	244
Mean Parasite															
Density +/- SD[c] PVa	4081.4 +/- 4290.5 (6)[d]			14 230 +/- 19 050 (26)			14 401 =/- 17 176 (21)			8233 =/- 11 103 (7)			1780 =/- 1447 (14)		
PVb	11 435 =/- 17.269 (12)			7805 =/- 8087 (25)			10 882 +/- 14 607 (47)			16 661 +/- 22 499 (19)			3931 =/- 7419 (36)		

A Cases with P.Vivax infection.

B Cases with P. Falciparum infection.

C All parties combined, data provided by 213 "good thick smears" (Pregnant 137; Pueperium 26; nonpregnant 50).

D Figures in Parentheses indicate the number of cases providing parasite density.

Parasite density was counted in only 213 patients out of 515 pregnant and non-pregnant) because 220 of the thick blood smears were not prepared correctly, 70 were poorly stained, and 12 slides were missing. Women of all parities were therefore grouped together in subsequent analyses of pregnant and non-pregnant women. Mean parasite densities were significantly higher in all three trimesters and the puerperium for the pregnant women, compared with non-pregnant women, for both *P.falciparum (P* <0.0001) and *P. vivax(P<0.05)* malaria. However, the parasite densities in the three

trimesters (all parities combined) did not show any statistically significant differences between trimesters for both types of infections.

The women with falciparum malaria were significantly more anaemic than the non-infected pregnant women (P <*0.0001;* df = 274) or the infected non-pregnant women (P <*0.001;* df = 271); the women with vivax malaria were also significantly more anaemic than the non-infected pregnant women *(P* <0.0001; df = 169) or infected non-pregnant women (P <0.005; df =166). Furthermore, among pregnant women (all parities combined), those infected with *P. falciparum* were significantly more anaemic than those with P.vivax (P<0.001; df=269). However, among non-pregnant women no such difference between *P. falciparum and P. vivax was* observed. when the association between malaria infection and anaemia was stratified by parity, primigravidae with *P. falciparum* were more anaemic than second gravidae and multigravidae, although only with the latter was the difference statistically significant (P <0.005; df = 97). However, in vivax infected pregnant women or non-infected pregnant women, the anaemia increased with increasing gravidae, but this was not statistically significant.

Three maternal deaths (two primigravidae and one multigravida) occurred in women who were infected with *P. falciparum* during the late third trimester (8-9 months). Two cases with *P.falciparum* infection died in the puerperium with anaemia (haemoglobin, 7.1 g/dl). Three abortions were recorded in women who were infected with *P. falciparum* during the first trimester (all primigravidae). Two stillbirths were recorded in women with *P. falciparum* (one primi- and one multigravida). Only one abortion and one stillbirth were recorded in vivax infected primigravidae. Among non-infected pregnant women, only one abortion (primigravida) and one stillbirth (multigravida) were recorded.

The clinical spectrum of 17 cerebral malaria cases (Po, 6; P_{1-2}, 7; $P_{3+,4}$) was much more severe. All of them presented with a history of fever which was associated with neurological signs and haemorrhage (5.8%), jaundice with severe anaemia (11.7%), convulsions (29.4%), and unconsciousness (53%). Of these 17 women, 12 died (P0, 5; P_{1-2}, 4; $P_{3+,3}$); among the 5 who recovered, one aborted and two had stillbirths.

The mean weights of the newborn babies from the non-infected pregnant women and infected pregnant women with different types of infections (all parities combined) Are shown in Table 1. The mean birth weight of the babies was significantly lower in the infected group than in the non-infected group (P<*0.0001;* df = 328); the mean birth weight of babies in the falciparum-infected group was lower than that in the vivax-infected group (P <0.05; df = 153). With regard to low birth weight, 89% of babies

weighed <2.5 kg in the infected group compared with 38% in the control group, which is highly significant statistically (P<*0.0001; Z* = 9.41).

Peripheral blood smears taken from the new-born babies were negative for malaria parasites in all the cases.

Discussion

Since very little information is available on the relationship between malaria infection and pregnancy in the Indian subcontinent, the present hospital based investigation on 365 pregnant women in central India is of special interest.

The highest malaria prevalence was among primigravidae, followed by second gravidae and multigravidae, which accords, with reports from Africa *(3)* *(13)*. While almost nothing was known about the incidence of *P. vivax* malaria, the prevalence of *P. falciparum* malaria among pregnant women was highest early in the second trimester with a decline towards term, and the incidence postpartum was usually similar to the pre-pregnancy level reported for Africa *(3, 12, 13).* An exactly identical pattern was shown by *P. vivax* malaria in our study, while the *P. falciparum* prevalence was nearly the same in all trimesters. The high prevalence of *P. vivax* in the second trimester was probably due to relapses, while similar prevalences of *P. falciparum* in all trimesters indicate primary infections, which suggests that the pattern of malaria may vary in areas of different endemicity, (3). A prospective controlled study in Chandigarh (5) showed that the parasite density was highest in the third trimester for both vivax and falciparum malaria, that parasite density remained high during the puerperium for both types of infections compared with the situation for non-pregnant women, and that parity had no influence on the parasite density. From our limited results, it is not possible to assess accurately the relationship between malaria parasite density and parity. Moreover, no conclusion can be drawn on the peak prevalence of parasitaemia for both parasite species since a much larger sample is needed to evaluate the effect of parity on parasite density.

Anaemia is a major problem among pregnant women in this region. The mean haemoglobin level was lower in primigravidae infected with *P. falciparum,* as reported in other malarious areas (14) (15) (16). In contrast, anaemia usually increases in vivax-infected women and in non-infected pregnant women with parity, with primigravidae being the least anaemic group. This is presumably because iron deficiency tends to increase as gravidity increases (17). It is unfortunate that the haemoglobin data from our pregnant and non-pregnant study subjects were incomplete because many women

feared the discomfort of blood sampling; we therefore do not have a more precise picture of the effect of anaemia in the infected and non-infected groups. Furthermore, since the etiology of anaemia in pregnancy is multifactorial, i.e. due to iron deficiency, folate deficiency and hookworm infection (18), the effect of malaria on this condition is difficult to ascertain. Quantification of the relative contributions of malaria, hookworm and malnutrition to anaemia is thus an important step in selecting appropriate control measures to prevent the adverse perinatal outcomes associated with anaemia in pregnancy.(19)

The association of low birth weight with malaria is well known (1), the mean birth weight of neonates born to infected mothers in our study being 350 g less than that of their counterparts born to non-infected mothers. This finding must be interpreted with caution, however, because it is malaria infection of the placenta that is associated with low-birth-weight infants. Peripheral parasitaemia does not mean that there is a placental parasite infection (3); similarly, we cannot be sure that clearance of parasites from peripheral blood indicates the elimination of placental infection.

Our findings also show that cerebral malaria is one of the common complications of severe falciparum malaria, with a high mortality during pregnancy. Furthermore, five maternal deaths, three abortions, and two stillbirths occurred among our uncomplicated *P. falciparum* cases. Unfortunately, all our referral cases had to be excluded because of incomplete records. Their omission from our analysis is likely to have underestimated the incidence of cerebral malaria and its complications during pregnancy in the local population.

Even though WHO (20) has recommended the use of an effective anti-malarial throughout pregnancy in an effort to prevent the adverse effects of malaria on the mother, fetus and newborn child, chemoprophylaxis is not administered routinely by the national malaria eradication programme (NMEP) in India. The only recommendation by the Ministry of Health is treatment of febrile episodes. Thus, all fever cases were initially given chloroquine in divided doses as first-line treatment. Patients who could not tolerate oral administration were given chloroquine by intramuscular injection. Chloroquine-resistant cases received a single dose of sulfadoxine-pyrimethamine. Cases resistant to all the above drugs, and cases of severe and complicated falciparum infection, were given intravenous quinine, as indicated in the NMEP schedule.

The available data from this hospital-based study show a high prevalence of cerebral malaria and anaemia in pregnant women, indicating the need for malaria

chemoprophylaxis. It should be routine policy to provide such chemotherapy to pregnant women through malaria clinics in endemic areas. This policy should be adopted despite the increased burden on limited medical budgets and administrative difficulties, because protection of this group of women at risk deserves serious consideration. However, most pregnant women do not usually go to the hospital or clinic until the second trimester.

Educational campaigns informing women of childbearing age about the dangers of malaria in pregnancy and the potential benefits available to expectant mothers would help improve the rate of early attendance at the clinic. The study results also show the need for changes in the Medical College Hospital and malaria clinics, e.g. introduction of training/workshops for all paramedical staff and laboratory technicians in order to obtain more reliable and precise data. However, the extent to which chemo-prophylaxis can reduce the risk of malaria during pregnancy will vary depending on the relative prevalences of vivax and falciparum malaria and on the level of drug resistance against *P. falciparum.*

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