# STUDIES ON MALARIA DURING PREGNANCY IN A TRIBAL AREA OF CENTRAL INDIA (MADHYA PRADESH)

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**Abstract.** In tribal villages of central India where malaria is highly prevalent (mesoendemic), this preliminary study was undertaken to determine the effects of malaria infection in a group of 456 pregnant women with or without fever. Only 96 women were found infected with malaria, of which *Plasmodium falciparum* accounted for 64% of the detected parasites, while *P. vivax* for the remaining 36%. There were no instances of cerebral malaria or death however, one abortion and four still births were recorded among 38 primigravid women. Only one neonate was found infected with *P. falciparum* on day 21 though parasitemia was not high. Anemia was commonly present in most of the women (80%).

Failure to clear *P. falciparum* parasitemia after a chloroquine regimen (25 mg/kg of body weight) was commonly observed. Persistent P. falciparum parasitemia was recorded in 8% cases. Poor response to chloroquine suggests the need to change the drug policy.

## INTRODUCTION

Pregnant women are especially vulnerable to malaria. Sinton (1935) recorded malaria as causing abortions, premature labor and still births, during an epidemic of 1908 in the Punjab in which malaria caused a 30% fetal wastage rate. Recent hospital based studies (Nair and Nair, 1993; Singh et al, 1995, 1996a) have confirmed the earlier observations that malaria during pregnancy can be an acute disease, life-threatening to both the mother and her fetus. However, the severity of malaria in pregnancy can vary in different circumstances (McGregor, 1984; Sholapurkar *et al*, 1988; Desowitz and Alpers, 1992). These studies were conducted in geographical regions that differ in climate, intensity of malaria transmission, use of malaria control measure and socio-cultural attitudes towards malaria. Since no study had been carried out in tribal areas, where malaria is highly prevalent, this preliminary study was undertaken in Mandla, central India (Madhya Pradesh), to determine the prevalence of malaria, its effects during pregnancy and to understand the feasibility of delivering malaria chemoprophylaxis to pregnant women. This information may be of assistance in determining priorities for preventative strategies.

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## MATERIALS AND METHODS

### Study area

This study was conducted in 25 tribal villages of Bizadandi PHC, District Mandla (MP) from April 1995 to January 1996 for a period of ten consecutive months. The study villages had a sparce population of 200 to 500 each, 85 to 90% of them being Gond tribals. These villages are located in rocky, hilly and undulating terrain with remains of mixed forest, 2.5-10 km from the main road. These villages are served by one primary health center and two subcenters. People are mostly illiterate, superstitious, scantily clothed and work mainly as casual laborers in forest nurseries or road construction work. Both *P. vivax* (Pv) and *P. falciparum* (Pf) infections are commonly prevalent (mesoendemic). *P. falciparum* is the dominant species from July to January, while *P. vivax* is so from February to June (Singh *et al*, 1996b). The peak precipitation occurs from mid June to mid September (rainfall 1,500-2,000 mm).

### Study group

The study involved a randomly chosen tribal

population of pregnant women aged 18 to 40 years. In all 456 pregnant women with or without fever, body pain and headache were registered and screened for malaria parasites. These women gave verbal consent to participate in the study. Personal and reproductive histories were obtained from each women registered in cohort.

In order to study parasite prevalence rates of malaria during pregnancy and puerperal period, these women in cohort were screened fortnightly at their residence irrespective of fever history. A blood film was taken, stained with JSB (Singh and Bhattacharji, 1944) and examined for malaria parasites. Those found positive for malaria, (presence of asexual parasites of either Pv or Pf or both in peripheral blood smear) were immediately treated with 25mg/kg chloroquine orally over 3 days *ie* 10 mg/kg dose on each of the first 2 days and 5 mg/kg dose on the third day, but chloroquine was not routinely administered upon registration. Asexual parasites and white blood cells were counted in 100 oil immersion fields and the parasite density per cubic millimeter ($mm^3$) of blood was calculated. Since both parasite species are prevalent in Mandla, women infected with both species were included in the study.

Blood was taken from these women for semi-quantitative estimation of hemoglobin (Hb) by the hematin acid method originally described by Sahli (1894). Mild and severe anemia in pregnant women were defined by Hb levels 7.0-10.0 g%/dl and < 7g%/dl of blood, respectively.

**Follow up**

The importance of malaria treatment was explained to all women. Blood smears were obtained from each registered pregnant woman of cohort fortnightly (2 weeks interval, unless stated otherwise) until parturition and during the 4 weeks period post partum. All women were visited in their homes and those who had parasitemia detected by thick smear were treated with chloroquine under observation and a thick smear was repeated one week later. If the repeat thick smear was not parasite free, women were treated with another dose of chloroquine and the thick smear was repeated one week later. At each following survey, the patients were asked whether they had fever with chill and rigor or headache or pain in the body and if so, for how long. These women were also given iron and folic acid but no chemoprophylaxis. Because women were sometimes absent from the village when the surveys were conducted, most only gave 5 to 6 samples each. [Among tribals, women have a major share of outdoor jobs like fetching firewood, fetching jungle produce etc. Jungle being provider of most of things needed for a tribal's sustainance they frequently visit jungle for various reasons as per their needs where it is difficult to trace them]. Attempts were made to follow all the 456 women recruited into this study but this proved difficult. Many women had gone to their parents village outside the study area to deliver their babies particularly primigravidae where they could not be approached. [It is a common custom in India that the first child is delivered at the woman's parents place]. These were excluded from the study (131). Information on the outcome of pregnancy was obtained from all the remaining 325 women. All women were encouraged to deliver at the health center, but not a single women went there for delivery. Hence slides at delivery could not be obtained from the mother and the placenta. Similarly due to traditional beliefs which preclude determining an infant's weight at birth, we were unable to determine the incidence of low birth weight.

However, birth weight of 10 neonates and blood smears from 100 infants were obtained within a week of delivery after much patient insistence and reasoning. Blood smears were again prepared from these infants after an interval of 2 weeks. Low birth weight was defined as newborns weighing < 2.5 kg, (Brabin *et al*, 1990a; Cot *et al*, 1993).

**Data analysis**

A woman was considered infected if asexual stage parasites of any species of malaria were detected in thick blood smears.

Parasitemia was defined as the presence of asexual parasites in thick blood smear. Persistent parasitemia was defined in a woman whose thick blood smear was never parasite free. Relapse was defined as the presence of *P. vivax* parasites on a thick smear among women who had been treated successfully and remained parasite free for 2 weeks after the treatment. Cases of persistent parasitemia were excluded in the analysis of the number of episodes of malaria parasitemia.

Differences in proportions were tested using the

Z test and the differences between the sample means were tested by *t*-test.

## RESULTS

Of 456 pregnant women (Table 1), 130 were febrile and 20 were afebrile but presented with a history of fever at the time of registration (45 primigravidae and 105 multigravidae). 59 (39%) were positive for malaria at registration, 21 were *P. vivax* (35.6%) and 38 were *P. falciparum* (64.4%), which also included four afebrile cases (all multigravidae). During fortnightly follow up of 325 women, an additional 37 women were found to be infected (11.4%) with malaria (14 Pv and 23 Pf). Out of a total of 96 cases, only 8 (2 Pv; 6 Pf) were in first trimester, 31 (8 Pv; 23 Pf) were in 2nd trimester and the remaining 57 (25 Pv and 32 Pf) were in 3rd trimester.

Of the 61 *P. falciparum*, 45 (73.8%) were carrying gametocytes with rings ($P_0$ 14; $P_{1\text{-}5}$ 31). The geometric mean parasite density (GMPD) was significantly higher ($p < 0.001$) in primigravidae (1,943.97 ± 8.4) compared to multigravid women (1,405 ± 12.9). Of the 61 *P. falciparum*, 12 cases remained parasitemic after treatment on day 7 but patients were all afebrile and parasitemia was not very high. The clearance of parasites was unrelated to initial parasite density. Out of 12, one patient refused to take another dose of antimalarials though she never refused to give a blood smear. The parasitemia was also not high (Fig 1). The remaining cases were given another dose of chloroquine and blood smears were made after one week. Parasitemia was still seen in five cases but in de-

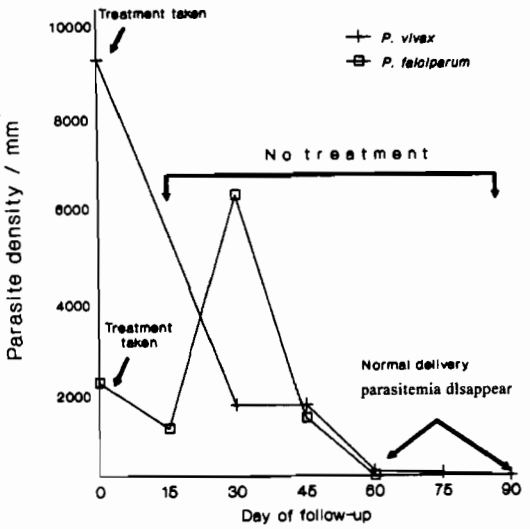


Fig 1–Persistant parasitemia in pregnant women (asymptomatic) who refused antimalarials.

Table 1

Prevalence of malaria in pregnant women.

| Parity | Population | Fever/ history of fever | Total* +ve | SPR | Pv | Pf | Pf% |
|---|---|---|---|---|---|---|---|
| P0 | 159 | 45 | 38 | 84.4 | 16 | 22 | 57.9 |
| P1 | 120 | 28 | 21 | 75.0 | 7 | 14 | 66.7 |
| P2 | 94 | 30 | 19 | 63.0 | 5 | 14 | 73.7 |
| P3 | 44 | 20 | 11 | 55.0 | 6 | 5 | 45.5 |
| P4 | 21 | 15 | 5 | 33.0 | 1 | 4 | 80.0 |
| P5 | 14 | 10 | 2 | 20.0 | 0 | 2 | 100.0 |
| P6 | 3 | 1 | 0 | 0.0 | 0 | 0 | 0.0 |
| P7 | 1 | 1 | 0 | 0.0 | 0 | 0 | 0.0 |
| Total | 456 | 150 | 96 | 64.0 | 35 | 61 | 63.5 |

* +ve = Positive for malaria parasite.
SPR = Slide positivity rate.
Pv = *Plasmodium vivax.*
Pf = *Plasmodium falciparum.*
Pf% = *P. falciparum* percentage.

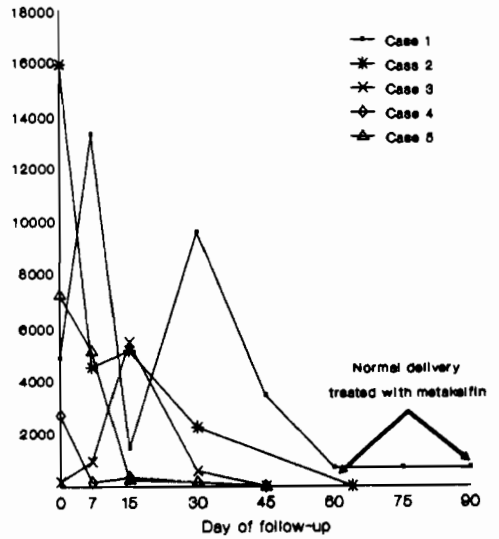


Fig 2–Persistent parasitemia in pregnant women (asymptomatic) who had taken chloroquine treatment.

scending order hence these cases were kept on suppressive doses of chloroquine (300mg) weekly until delivery. All these five cases showed persistent parasitemia till delivery and remained afebrile throughout (Fig 2). After delivery 3 became aparasitemic without further treatment. The remaining two were treated with pyralfin. [3 tablets of pyralfin given as a single dose (sulfadoxine, 1,500 mg-pyrimethamine 75 mg). Manufactured by Lupin laboratories (Aurangabad, India]. All 6 cases with persistent parasitemia, including the one who refused treatment, were multigravid women.

Of the remaining 55 *P. falciparum*, 23 (42%) women presented with more than one episode of malaria parasitemia after taking chloroquine. Only 10 (43%) of the 23 women with parasitemia had a history of recent fever or other symptoms which they perceived as malaria. Out of 13 asymptomatic cases only 3 were primigravidae and remaining 10 were multigravid women. About 22% had expenenced 2 episodes of *P. falciparum* parasitèmia, 18% had 3, another 3.6% had four episodes and 5.4% had experienced five or more episodes of parasitemia till the duration of pregnancy and puerperal period (Table 2). There was no significant difference in the number of infections experienced by primigravidae and multigravidae. In only two women *P. falciparum* parasites were seen after delivery on D15 along with classical fever. Only one neonate had fever with *P. falciparum* (asexual and sexual stages) on D21 (parasite density 180mm$^3$, weight, 2.8 kg). Abortion occurred only in one case and still birth in three cases. All four were primigravid women.

Of 35 *P. vivax* (P0-16, P1-5-19), parasite density was significantly higher ($p < 0.001$) in primigravidae (GMPD 1,432.32 ± 8.6) as compared to multigravidae (899.64 ± 4.5). One multigravid woman refused to take chloroquine after initial treatment and remained parasitemic till delivery (Fig 1). Out of 34, relapse parasitemia or reinfection (Table 2) appeared within 2 months in 4 women,

Table 2

Characteristics and follow up of registered pregnant women with malaria.

| Species | No. of women parasitemic* on follow up visit | | | | | |
|---|---|---|---|---|---|---|
| | Day 15 | Day 30 | Day 45 | Day 60 | Day 75 | Day 90 |
| *P. vivax*** 32 | 0 | 1,234.54 ± 1.3 | 1,515 ± 0 | 100 ± 0 | 94.86 ± 2.8 | 450 ± 0 |
| | (0) | (2) | (1) | (1) | (2) | (1) |
| *P. falciparum* 55 | 896.73 ± 4.07 | 1,067.11 ± 4.93 | 975.79 ± 1.39 | 270 ± 0 | 1,293.39 ± 9.72 | 0 |
| | (12) | (10) | (2) | (1) | (2) | (0) |

Figures in parenthesis indicate the number of pregnant women.

* Geometric mean parasite density/mm$^3$.

** 2 Pv were found mixed with Pf within 45 days. They were not included in the Table. One Pv and 1 Pf refused to take chloroquine hence not include in this Table.

Table 3

Hemoglobin level in pregnant women with and without malaria (*P. falciparum*).

| Parity | Total cases | Hb g%/dl | | |
|---|---|---|---|---|
| | | < 7 | 7.1-10 | > 10.1 |
| With malaria | | | | |
| $P_0$ | 25 | 1 (4) | 19 (76) | 5 (20) |
| $P_1$-$P_5$ | 40 | 3 (7.5) | 32 (80) | 5 (12.5) |
| Without malaria | | | | |
| $P_0$ | 37 | 1 (2.7) | 20 (54) | 16 (43.2) |
| $P_1$-$P_5$ | 79 | 2 (2.5) | 55 (69.6) | 22 (27.8) |

Figures in parenthesis indicate percentages.

Table 4

Hemoglobin level in pregnant women* with persistent parasitemia and birth weight of neonates.

| Parasite species | Hemoglobin g%/dl | | Birth weight within a week (kg) |
|---|---|---|---|
| | Initial | One month later | |
| *P. falciparum* | 7.4 | 5.1 | 2.30 |
| *P. falciparum* | 9.2 | 8.0 | 2.45 |
| *P. falciparum* | 8.4 | 7.0 | 2.40 |
| *P. falciparum* | 10.0 | 7.5 | 2.45 |
| *P. falciparum* | 7.5 | 6.0 | 2.25 |
| *P. falciparum* | 7.5** | 5.3 | 2.00 |
| *P. vivax* | 10.00*** | 8.2 | 2.40 |

* All multigravid women.

** *P. falciparum* infected women who refused to take treatment.

*** *P. vivax* infected women who refused to take treatment.

and within 3 months in another 3 women. Only one still birth was recorded in one primigravid woman. During follow up, *P. vivax* infection in 2 women was found to be mixed with *P. falciparum* within 45 days. Further follow up of these 2 cases showed only parasites of *P. falciparum* which were treated with chloroquine successfully.

While in remaining 229 pregnant women without malaria infection, abortion occurred in one primigravidae and one multigravidae. Only one multigravida died at the time of delivery.

Table 3 showed that 80% of primigravidae and 87.5% of multigravid women had anemia (< 10 g%). In pregnant women without malaria, the prevalence of anemia was high as well, 57 and 72% respectively in primigravidae and multigravid women. In both these groups, multigravid women had a slightly higher prevalence of anemia than primigravidae, though the difference was not statistically significant. However, the overall prevalence of anemia was significantly higher ($Z = 35.4$) in pregnant women with malaria as compared to pregnant women without malaria. To examine further the association of malaria parasitemia and anemia, hemoglobin was measured in cases with persistent malaria (including two women who refused treatment) with the remaining 89 cases without persistent parasitemia. All pregnant women with persistent parasitemia were anemic and their anemia had further worsened between 5-8 g% (Table 4). Their babies were also of low birth weight

(2,000-2,500 g), as measured within 7 days of delivery. In pregnant women without persistent parasitemia the hemoglobin level was increased by 1 or 2 g% in 75 and stable in 14 cases (data not shown).

The study further revealed that not a single woman went to hospital for delivery. Help of traditional birth attendants was taken by 59% women. Those who refused to take antimalarials were asked to give specific reasons for not doing so. Both stated that there was no need to take the medication since they were not ill.

## DISCUSSION

The results of this study pose a problem for health policy makers since chloroquine failed to clear persistent parasitemia in 8% women indicating that chloroquine resistance is common in the area as recorded earlier (Singh *et al*, 1989; Singh and Shukla, 1990). The failure rate among these 8% suggested that weekly suppressive doses of chloroquine would not effectively maintain the peripheral blood free of parasite and reduce the parasite blood load, particularly in the placenta (Steketee *et al*, 1987). The purpose of regular antimalarial chemoprophylaxis during pregnancy is to clear or prevent placental parasite infections, since it is the placental infection that is associated with delivery of low birth infants (McGregor, 1984). Though we have no data on placental parasitemia from this area, nevertheless it is certain that persistence of parasites in the peripheral blood bodes ill for placental parasite clearance (Steketee *et al*, 1987). However, this study also indicates absence of acute effects of *P. falciparum* in pregnant women, may be due to the immune competence of the host population which is further confirmed by consistently low parasite density (Nosten *et al*, 1991). Similar results were also recorded by other investigators (Edington and Gilles, 1969; Menedez, 1995). Further, about 30% women presented with one or more episode of parasitemia (average $1.6 \pm 1.09$) during pregnancy and the puerperal period. Although some of these episodes of parasitemia were probably due to the recrudescence of a chloroquine resistant parasites, the possibility of reinfection can not be ignored as two women originally having *P. vivax* were found infected with *P. falciparum* during subsequent follow up. A similar finding is evident in the data presented by Nosten *et al* (1991).

In endemic areas of Africa, an increase in malaria attacks has been observed during the first trimester of pregnancy (Brabin, 1983; Gilles *et al*, 1969; Fleming *et al*, 1969; Brabin *et al*, 1990b). In contradiction, we found the lowest prevalence of both species of malaria during first trimester and highest prevalence in third trimester. However, in this study a majority of women came only during the last trimester and some are likely to have experienced malaria before being registered. Different results might have been obtained had their registration been done at the beginning of pregnancy.

In contrast to a previous report (Singh *et al*, 1995) anemia was more frequent in multigravidae than in primigravidae, indicating that factors other than malaria may be important in producing anemia in this area. This is further supported by the fact that more than 60% pregnant women without malaria were also anemic which might be due to dietary inadequacy. Thus it appears that highly prevalent anemia is of nutritional in origin which is further aggravated by pregnancy (Isah *et al*, 1985). Thus additional indepth studies are required to assess the problem of anemia during pregnancy in this area. Interestingly, we observed that all pregnant women with persistent parasitemia and severe anemia were multigravid and they refused to go to hospital as they had no clinical signs. Even though these women were offered assistance with transport and referral to a good hospital for delivery, none had gone. It is of interest to note that all delivered at home apparently normally. Unfortunately, the birth weight of new borns could not be measured within 24 hours after delivery but on day 7 all infants born to women with persistent parasitemia were found to be of low birth weight. Absence of clinical symptoms in multigravid women in endemic areas was also reported by McGregor (1987) and Brabin (1991). The percentage of asymptomatic carriers was not high in this population, as only 1.2% non pregnant women of child bearing age were found to be asymptomatic carriers, (unpublished data).

WHO (1986) recommended early treatment of clinical malaria and chemoprophylaxis using an effective antimalarial throughout pregnancy. Effective strategies for control of malaria during pregnancy require an effective drug for treatment and chemoprophylaxis. In the absence of an alternative, chloroquine is considered reasonably effec-

tive and safe in the chemotherapeutic and chemoprophylactic control of malaria in pregnant women (Bruce Chwatt, 1983). However, in endemic areas like this, it is not known whether prophylactic doses of chloroquine will be adequate to prevent pregnant women from malaria infection or whether chloroquine prophylaxis can clear asymptomatic parasitemias experienced by many pregnant women. Moreover, in areas where both chloroquine resistant *P. falciparum* and *P. vivax* are highly prevalent, malaria treatment and chemoprophylaxis during pregnancy becomes more complex. The problem faced is that in such areas a malaria control strategy which relies on chloroquine chemoprophylaxis will have limited efficacy in limiting *P. falciparum* placental infections (Nahlen, personal communication). Whereas presumptive treatment with sulphadoxine-pyrimethamine is effective in preventing *P. falciparum* infection, it will have limited efficacy against *P. vivax*. Therefore, further studies are required to determine whether the chloroquine prophylaxis was effective in the control of malaria during pregnancy in an area where both chloroquine resistant *P. falciparum* and *P. vivax* are common.

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