FALCIPARUM MALARIA AND PREGNANCY: RELATIONSHIP AND TREATMENT RESPONSE

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INTRODUCTION

Malaria is reported to have a profound deleterious effect on pregnancy causing abortion, intrauterine foetal death, premature delivery, and maternal death (Lawson, 1967). The increase in prevalence of malaria and of higher parasite density in pregnant women is well documented in studies carried out mostly in Africa (Gilles *et al.*, 1969; Bray and Anderson, 1979; McGregor *et al.*, 1983; Brabin, 1983) and a few studies carried out in Southeast Asia (Menon, 1972; Looareesuwan *et al.*, 1985). We carried out this hospital-based study in Taunggyi, which is 4712 feet above sea level. Malaria cases presenting to the hospital come in from surrounding endemic areas 10 to 50 miles around with an elevation of 2000 to 3000 feet. The areas are hyper endemic areas with a transmission season from June to November. The annual malaria morbidity and mortality in the medical wards of this hospital are: 548/7 (1981); 813/14 (1982); 1109/29 (1983); 1018/24 (1984); 1196/26 (1985); 1105/19 (1986). The main objectives of this study were to identify the relationship of pregnancy to degree of parasitaemia (parasite density), and to study response to treatment in pregnant women with malaria.

MATERIALS AND METHODS

Included in the study were 42 pregnant patients (age 16–40 years) and 51 non-pregnant females with malaria who were admitted to the medical wards of Sao San Htun Hospital and to the obstetrics wards of Women and Children's Hospital, Taunggyi during June 1985 through December 1986. All patients had asexual forms of *Plasmodium falciparum* in their peripheral blood film. All were hospitalized for at least 7 days, and were followed up weekly after discharge. Pregnant patients were requested to return for delivery to document outcome of pregnancy.

A full clinical history and physical examination on each patient was carried out, including a detailed obstetric assessment with estimation of gestational age. Routine obstetric care was carried out daily on all pregnant patients admitted to the study. Detailed records of patients were kept, including body temperatures (taken 4 hourly till patient was afebrile for 24 hours, and then twice a day). Thick and thin peripheral blood films were examined every 12 hours. Quantitative parasite count were done according to the method described by the WHO (1984). Routine laboratory tests on

blood and urine were also carried out. Blood was taken on blotting paper from 36 pregnant mothers and sent to the Immunology Division of Directorate of Medical Research, Rangoon for IFAT titres. The results were plotted against parity and gestation period.

Patients were randomised to receive either quinine or amodiaquine treatment groups depending on clinical severity and parasite density. Quinine dihydrochloride (10 mg salt/kg body weight equivalent to 8.3 mg base/kg body weight) was given at 8 hourly intervals for 7 days orally or by infusion, depending on the clinical condition of the patient. Amodiaquine hydrochloride (150 mg base, UNICEF) was given orally in a total dose of 25 mg/kg body weight divided over three days. Only those who were vomiting and could not swallow pills quinine infusion was given initially. *In vitro* sensitivity tests could not be done in this hospital, neither the estimation of blood levels of antimalarial drugs, although the urine of those included in the study were tested for quinine, 4-amino quinolines and sulfonamides prior to inclusion into the study.

Data processing was carried out using CRISP (CRunch Interactive Statistical Package) software on an IBM PC XT computer.

RESULTS

Among 42 pregnant patients, 23 were treated with quinine and 19 with amodiaquinei. Of the 51 non-pregnant female patients, 26 were treated with quinine and 25 with amodiaquine. The mean age, and initial parasitaemia were comparable in all treatment groups (Table 1). There was no statistically significant difference in fever clearance time or parasite clearance time among pregnant and non-pregnant patients irrespective of whether quinine or amodiaquine was given. Also, there was no significant difference in the above parameters in response to quinine or amodiaquine among both pregnant and non-pregnant women with malaria.

Of 42 pregnant patients, 17 (40.5%) were primigravidae, 13 (31.0%) were of parity 1 to 3, and 12 (28.6%) were parity 4 or more. Table 2 shows that parasite density, fever clearance time and parasite clearance time were the same among pregnant patients with malaria whether it was the first or a subsequent pregnancy.

Among the primigravidae, 9 (52.9%) were in their second trimester when they were admitted for malaria. Overall pregnant patients 21 (50%) were in their second trimester when hospitalized for malaria. When the patients in early second trimester (13–18 weeks) were compared with those in the late second trimester (19–24 weeks), (Table 3) it was found that although parasite density and fever clearance time were similar, there was a statistically significant prolongation of parasite clearance time among patients in the late second trimester.

Due to difficulties in travel and transport, only 4 patients sought hospital delivery. Another 4 patients were delivered by midwives. All 8 were normal spontaneous vaginal deliveries. The outcome of 20 pregnant patients could not be traced. Ten patients had spontaneous termination of their pregnancy during their stay in hospital for the treatment of malaria. Also, there was one patient who died of fulminant hepatic failure from concurrent viral hepatitis, producing a still born child, and three premature deliveries, one baby weighing 2 pounds and 6 ounces died two days after birth. No conclusion could be drawn from the scatter dia-

Table 1

Response to treatment in pregnant and non-pregnant patients with malaria.

Parameters	Pregnant patients	Non-pregnant patients
Quinine group		
Age (years)	26.7 ± 1.2*	32.1 ± 1.5
Initial parasitaemia (log mean counts/cmm)	4.3 ± 0.3	4.4 ± 0.1
Fever clearance (hours)	59.3 ± 8.2	65.5 ± 6.9
Parasite clearance (hours)	93.7 ± 5.2	99.5 ± 5.1
Amodiaquine group		
Age (years)	24.3 ± 1.0	22.9 ± 1.6
Initial parasitaemia (log mean counts/cmm)	3.9 ± 0.2	3.9 ± 0.1
Fever clearance (hours)	45.2 ± 8.4	36.3 ± 4.3
Parasite clearance (hours)	99.4 ± 6.9	97.9 ± 5.7

* Mean ± S.E.

Table 2

Comparison of parasite density, fever clearance and parasite clearance in primigravidae and other parities of 42 patients.

Clinical parameter	Primigravidae	Other parities	P Value
Parasite density (per cmm)	$5.67 \times 10^4 \pm 2.30 \times 10^4$*	$7.56 \times 10^4 \pm 4.57 \times 10^4$	NS
Fever clearance (hours)	81.3 ± 19.2	58.5 ± 12.1	NS
Parasite clearance (hours)	142.4 ± 23.8	112.3 ± 10.1	NS

* Mean ± S.E.
NS = not significant

Table 3

Comparison of parasite density, fever clearance time and parasite clearance time of 21 patients during early second trimester (13–18 weeks) and late second trimester (19–24 weeks).

Clinical parameter	Early second trimester	Late second trimester	P Value
Parasite density (per cmm)	$3.87 \times 10^4 \pm 3.28 \times 10^4$	$6.39 \times 10^4 \pm 3.04 \times 10^4$	NS
Fever clearance (hours)	59.4 ± 15.1	83.4 ± 23.1	NS
Parasite clearance (hours)	90.9 ± 9.4	158.4 ± 25.2	< 0.05

Values in Mean ± S.E.

gram of the IFAT titres plotted against parity and gestation period.

Most of the pregnant women who were entered in this study lives in the endemic area and are probably semi-immune subjects. Malaria does increase the rate of abortion, intra-uterine foetal death, still birth and maternal mortality, but probably due to pre-existing immunity we found no difference in response to treatment in pregnant and non-pregnant group.

DISCUSSION

The prevalence of malaria is highest among the primigravida (40% of all pregnant patients). Malaria was most frequent in the second trimester regardless of parity (50% of all pregnant patients with malaria). Our findings are similar to those reported from Gambia, Kenya, and Nigeria (Brabin, 1983).

No differences in the parasite density, fever clearance and parasite clearance times were found among the primigravidae and multigravidae. This differs from a study in Kenya (Brabin, 1983) where enhanced clearance of malaria was demonstrated in multigravidae compared to primigravidae. It may be due to the age of patients: our patients were younger in the primigravidae group. Geographical and racial differences may also be partly responsible. Kortman (1972) in Tanzania found little difference between the first and subsequent pregnancies, while in Malaysia, most of the severe cases were observed in the multigravidae patients (Menon, 1972).

The second trimester of pregnancy bears the brunt of malaria infection during pregnancy. Among multigravidae, Brabin (1983) reported peak prevalence in multigravidae at 13 to 16 weeks gestation; Bray and Anderson (1979) reported that percentage prevalence and parasite density were high during pregnancy at 24 weeks and over. In our patients the parasite density was higher in late second trimester (though not significantly so,

Table 3), and these latter patients a significantly longer time for clearance of parasitaemia ($P < 0.05$, Table 3). The reason for this delayed parasite clearance in the late second trimester of pregnancy is not clearly known: anaemia and splenomegaly which occurs during this period may play a part. Gilles *et al.*, (1969) found that anaemia developed invariably between 16–24 weeks and that red cell survival surface counting studies showed a gradual increase in the excess count over the liver and the spleen. Most of the African field studies showed maximum parasite rates in the early second trimester (Lawson, 1967, Brabin, 1983). However, Fleming *et al.*, (1969) in Nigeria observed no correlation between parasitaemia and period of gestation in a selected group of 11 patients hospitalized for anaemia.

Either chloroquine or amodiaquine is recommended (Lawson, 1967) for the treatment of falciparum in pregnancy. Looareesuwan *et al.*, (1985) on the other hand showed that quinine infusion can be given safely to treat severe falciparum malaria during late pregnancy, when foetal and maternal distress were reduced as temperatures abated. We used amodiaquine instead of chloroquine as there was wide-spread chloroquine resistance in the Shan States. Comparison of the proportion of amodiaquine failures among pregnant and non-pregnant patients, and also comparison of quinine failures among these two groups showed no significant differences. This suggests that pregnancy does not necessarily impair body response to antimalarial drugs, and also that drug resistance in pregnant women occurred to the same degree as that prevailing in the same geographical region.

SUMMARY

Fifty-two patients with falciparum malaria during pregnancy were studied in Taunggyi, Shan States, Burma, during the period of April 1985 through December 1986. Severely ill cases were all treated with quinine, but uncomplicated cases were randomised to receive either quinine or amodiaquine. Fifty-one age-matched non-pregnant female patients were also randomised to receive either quinine or amodiaquine. All clinical and laboratory parameters were comparable between pregnant and non-pregnant group of patients. Falciparum malaria was most frequent among primigravidae, and occurred most frequently in the second trimester for all parities. There were no differences in parasite density, fever clearance and parasite clearance between groups with different parity or gestational period. Quinine and amodiaquine treatment were equally effective. The outcome of pregnancy with and without anti-malarial prophylaxis is discussed.

ACKNOWLEDGEMENTS

The authors we are greatly indebted to Dr. Mary Krasu, consultant obstetrician and gynaecologist and medical and nursing staff of Obstetrics Wards, Women and Children's Hospital, Taunggyi, for collaborating in this study, and to Dr. Khin Maung U, Head, Clinical Research Division, Department of Medical Research, Rangoon, for data processing and statistical analysis. This study was funded under a "Clinical Research Grant" by the Department of Medical Research, Rangoon.

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