Berkala Ilmu Kedokteran
Vol. 36, No. 1, 2004

Risk predictors for malaria in pregnancy and the role of chloroquine in low endemic area

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ABSTRACT

Iwan Dwiprahasto - ***Risk predictor for malaria in pregnancy and the role of chloroquine in low endemic area***

Background: Pregnant women in malaria-endemic areas are uniquely susceptible to infection with *Plasmodium falciparum* and this susceptibility is greatest during first pregnancies. Malaria causes serious complications in pregnant women, especially in those who have a low level of acquired immunity before pregnancy.
Objective: to assess the risk predictors for malaria during pregnancy and the role of chloroquine in low endemic area of malaria in Jepara district
Design: A longitudinal study of all pregnant mother was carried out in Batealit and Mayong I subdistricts of Jepara district between June 1997-August 1999. All pregnant women were screened for peripheral parasitaemia through active surveillance. Women who had parasitaemia were treated with chloroquine for 3 days. Blood smears were then examined on days 4, 7, 14 and 21 after completion of the chloroquine course. All women irrespective of the blood smear results at enrolment were followed up once every two weeks until delivery.
Results: Among 3099 pregnant women enrolled in the study, only 58 women had malaria infection, giving an incidence rate of 1.9/100 pregnant women. In this study low income is a significant risk predictor for malaria (OR= 11.03; 95%CI: 3.91-31.08). Women who had reported a history of malaria or history of taking antimalarial drugs 6 months before their last menstrual period (LMP) showed an increased risk of developing malaria during pregnancy (OR= 10.56; 95%CI: 4.57-23.72 and OR = 10.90; 95%CI: 4.48-25.61) respectively. Among those infected by *P.falciparum* and *P. vivax* and treated with chloroquine, complete parasite clearance was found in day 7.
Conclusions: This study shows that low income, history of malaria within 6 months before LMP and history of taking antimalarial drugs within 6 months before LMP are best predictor for malaria in pregnancy in low endemic area. This study also shows that chloroquine is still effective for treating malaria falciparum in pregnancy in Batealit and Mayong I subdistricts, Jepara

Keyword: malaria – pregnancy – low endemic area – risk-predictor – chloroquine

ABSTRAK

Iwan Dwiprahasto - *Penanda risiko selama kehamilan dan peran klorokuin di daerah dengan endemisitas rendah*

Latar belakang: di daerah endemik malaria, wanita hamil memiliki kerentanan khusus untuk terinfeksi *Plasmodium falciparum* dan kerentanan ini lebih tinggi pada kehamilan yang pertama. Pada wanita hamil, khususnya pada mereka yang imunitasnya rendah sebelum hamil, malaria memberi konsekuensi serius pada ibu dan janinnya.
Tujuan: mengetahui penanda risiko malaria selama kehamilan dan peran klorokuin pada ibu hamil di daerah dengan endemisitas rendah, Jepara.
Metode: Studi longitudinal dilakukan terhadap seluruh ibu hamil di kecamatan Batealit dan Mayong I, Jepara antara Juni 1997-Agustus 1999. Skrining terhadap malaria pada ibu hamil dilakukan melalui

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surveillance. Jika terbukti parasitemia, subyek diterapi dengan klorokuin selama 3 hari. Pemeriksaan darah apus selanjutnya dilakukan pada hari ke 4, 7, 14 dan 21 setelah terapi. Pemantauan terhadap seluruh ibu hamil dilakukan setiap 2 minggu sekali mulai saat rekruitmen hingga melahirkan.
Results: Dari 3099 subyek, hanya 58 yang terinfeksi malaria, dengan angka insidensi 1.9/100 ibu hamil. Sosio-ekonomi rendah merupakan penanda risiko malaria yang signifikan (OR= 11.03; 95%CI: 3.91-31.08). Riwayat malaria (OR= 10.56; 95%CI: 4.57-23.72) atau riwayat minum obat antimalaria dalam 6 bulan sebelum hari pertama menstruasi terakhir (OR = 10.90; 95%CI: 4.48-25.61) meningkatkan risiko terjadinya malaria selama kehamilan. Subyek penderita malaria menunjukkan respons klinis dan laboratoris yang baik terhadap terapi klorokuin.
Simpulan: Sosio-ekonomi rendah, riwayat malaria dan riwayat minum antimalaria dalam 6 bulan terakhir sebelum HPM merupakan penanda risiko yang penting untuk terjadinya malaria selama kehamilan. Di daerah dengan endemisitas rendah, klorokuin masih efektif untuk mengatasi malaria pada ibu hamil.

(B.I.Ked. Vol. 36, No.1: 45-52, 2004)

BACKGROUND

In high transmission areas such as sub-Saharan Africa, women in their first pregnancy are most vulnerable to malaria. The risks associated with malaria infections in non-immune pregnant women include spontaneous abortion in up to 60 per cent of cases and a maternal mortality rate of up to 10 per cent.[1]

The prevalence of malaria was lowest at the first trimester for all parities, with peak prevalence in first pregnancy occurring at 16-20 weeks.[2] It would appear, therefore, that women have an increased prevalence and severity of malaria early in pregnancy, with a likelihood of recovery to non-pregnant levels at, or close to, the time of delivery.

In endemic areas malaria during pregnancy is frequently asymptomatic.[3,4] Screening women for malarial parasitaemia cannot exclude malaria since women may show a negative film of peripheral blood when they have placental parasitaemia.[5,6]

Compared with non-pregnant women, pregnant women are at increased risk of malaria infection and its disease consequences in settings of both low and high transmission of malaria.[7,8] However, the particular manifestation of malaria differs between settings where residents have significantly different levels of immunity. In settings with low levels of malaria transmission, women of reproductive age have relatively little acquired immunity, and all pregnant women are comparably susceptible to malaria.[9]

Studies in malaria endemic regions have reported an association between maternal anaemia and low birth weight.[10-13] Several studies have also suggested that placental infection with *P. falciparum* is associated with low birth weight.[14] In a study of 6,427 singleton births in The Gambia, McGregor[15] and colleagues found that the mean birth weight of babies born to mothers with placental malaria was 170 g lesser than that of babies born to mothers without placental malaria. However, this weight difference was reported to be statistically significant only among primigravidae.

This study was aimed to assess the risk predictors for malaria during pregnancy and the role of chloroquine in low endemic area of malaria in Jepara district.

STUDY DESIGN

A longitudinal study was carried out in 2 subdistricts of Jepara district, i.e. Batealit and Mayong I. All pregnant women in the sub-districts of Batealit and Mayong were screened for peripheral parasitaemia through active surveillance or during their antenatal care at village maternity clinics or antenatal clinics at Primary Health Centres (PHCs). Women who had parasitaemia were treated with chloroquine (QC) for 3 days. Blood smears were then examined on days 4, 7, 14 and 21 after completion of the chloroquine course. All women irrespective of the blood smear results at enrolment were followed up once every two weeks until delivery and blood slides were examined if they gave a history of fever during one week prior to the date of follow up.

Identification of pregnant women

Malaria Workers (MW) and Village Health Workers (VHWs) identified pregnant women at hamlet level through an active surveillance system. They recorded the identification particulars of pregnant women and interviewed them using structured forms. Village midwives recruited pregnant women at village maternity clinics and information obtained were reported to the Field coordinator who then collated these data and reported to the Sub-district co-ordinator.

Eligible women enrolled in the study were informed about the study objectives and procedures. Pregnant women who agreed to participate in the study signed written informed consent. At the time of enrolment, data on women's identification, demographic, socio-economic, medical and obstetric characteristics, were collected using a structured questionnaire.

At enrolment blood samples were taken by fingerprick for estimating haemoglobin and to prepare a thick blood smear. Two thick malaria blood smears were made for cross checking. If parasitaemia was detected, pregnant women were visited at home and the first, second, and third dose of chloroquine were taken in the presence of a sub-district co-ordinator or senior midwife in charge, on days 1, 2, and 3 respectively. The drug schedule, therefore, was as follows: (1) day 1 (at enrolment): CQ 10 mg base/kg body weight; (2) day 2: CQ 10 mg base/kg body weight; (3) day 3: CQ 5 mg base/kg body weight; (4) day 7, 14: thick blood smear (if parasites detected on day 1)

If a woman reported at any time during the 14 day follow-up period with symptoms suggesting persistence of malaria, a blood film was collected and the patient was managed in the same way as if a positive blood film had been obtained on days 7 or day 14.

Malaria worker (MW) and VHW visited pregnant mothers at their respective villages once every two weeks. Each malaria worker and VHW was given a record book containing women's name, age, address, date of first visit to ANC, history of diseases during pregnancy, and previous obstetric history and the expected date of delivery, in order to facilitate follow up. Any symptoms reported by the subjects within the last two weeks were recorded. If fever or malaria-related symptoms were reported by pregnant woman within the last 7 days, a thick blood smear was taken by a MW for parasite examination. All slides made during follow up visit were labelled and sent to the PHC for staining and examination on the same day.

There were three entries where perinatal outcomes were recorded, i.e. through the TBA, MW or senior midwives. The TBA, VM, or senior midwives who conducted the delivery took blood samples from the maternal site of the placenta for parasite examination. Data on delivery from TBA or village midwives were reported to the VHW or MW at the respective village who then sent the report to the Sub-district co-ordinator within 24 hours. Information on delivery included name of mother, address, name of husband, name of TBA or VM, and day and time of delivery.

This study was carried out after obtaining approval from the Ethical Committee for Biomedical Research in Human Subject, Gadjah Mada University-Yogyakarta and the Ethical Committee of the London School of Hygiene and Tropical Medicine, London.

RESULTS

A total of 3099 pregnant women were enrolled in the study between June 1997 and August 1999. Forty eight women (1.55%) who had reported their pregnancy at 6-10 weeks of gestation were found not to be pregnant, 63 (2.03%) moved from the study area, and 18 (0.6%) refused follow-up Twenty five pregnant women were referred to the district hospital and no further data could be obtained, and 4 (0.13%) died before delivery (one due to a traffic accident and the other three due to excessive bleeding after failure to deliver a breech presentation at home).

The characteristics of pregnant women who participated in the study are summarized in **Table 1**. The mean maternal age of pregnant women was 24.31 years, with the youngest 11 years old and the oldest 48 years. More than a one third (41.1%) of the subjects were primipara and the rest were secundi (28.3%) and multiparous (30.6%). The table shows that pregnant women were enrolled

mostly in the first trimester (46.1%) followed by 2nd and 3rd trimester, at 46.1, 35.9 and 18% respectively. The mean gestational age at enrolment was 18.5 weeks. The socioeconomic status of pregnant mother was equally distributed between high (29.3%), middle (38.5%) and low (32.2%) categories based upon monthly income reported by the family.

TABLE 1. Characteristics of pregnant women

Characteristics	No. and (%)
Maternal age (Mean ± SD)	24.31 ± 5.73
Parity	
0	1274 (41.1)
1	878 (28.3)
2+	947 (30.6)
Gestation AGE AT ENROLMENT (mean ± SD)	18.5 ± 6.77
1st trimester	1430 (46.1)
2nd trimester	1112 (35.9)
3rd trimester	557 (18.0)
Reported income of family	
High (>300,000 rupiah)	640 (29.3)
Middle (200-300,000 rupiah)	839 (38.5)
Low (30-199,999 rupiah)	703 (32.2)
Maternal education	
Primary	2173 (70.1)
Secondary	729 (23.5)
Secondary +	197 (6.4)
Occupation	
Housewife	1264 (40.8)
Manual job	1519 (49.0)
Sedentary	316 (10.2)
History of malaria within 6 months before LMP*	61 (2.0)
History of taking CQ or SP within 6 months before LMP*	51 (1.7)
Height (cm); mean ± SD	153.55 ± 4.97
Weight at delivery (kg.); mean ± SD	49.59 ± 5.29

*LMP= last menstrual period; CQ=chloroquine; SP= sulphadoxine-pyrimethamine

A majority of women had primary school education (70.1%) and a few had tertiary level education. There were more women who worked than those who did not. It is common in the study area for women to work as a part timer in furniture companies as the study area is one of the biggest teakwood furniture producers in Indonesia.

Only a small number of women (2 %) reported a history of malaria within 6 months before their last menstrual periods (LMP). A similar proportion had also taken chloroquine within six months before their LMP.

Incidence of malaria among pregnant women

During the study period only 58 women had malaria infection, giving an incidence rate of 1.9/ 100 pregnant women. Out of 58 cases, almost half (24) were detected at enrolment, one-fourth (15) during follow up visit and the rest (19 cases) were malaria positive at delivery. *P. falciparum* accounted for 30 cases while *P. vivax* was responsible for 28 cases. During follow up visits, parasite examination was undertaken in 168 women who complained of

malaria related symptom. Malaria parasites were detected in 15 out of 168 thick blood smear to give a slide positivity rate of 8.93%

Risk predictors for malaria

TABLE 2 shows risk predictors for malaria. During the study period 58 women were found to have malaria, i.e. 24 were detected at the first antenatal visit, 15 during follow up visits and 19 at delivery.

A univariate analysis of risk predictors for malaria was carried out to look at independent variables which might correlate with the occurrence of malaria. Compared to multigravidae (parity > 2) primigravidae and secundigravidae showed a greater risk of malaria, but the differences was not statistically significant. Pregnant women who were enrolled in the 1st trimester showed a greater risk of developing malaria than those enrolled later but the differences was not statistically significant (OR=1.35; 95%CI: 0.89-2.06).

TABLE 2. Risks predictors for Malaria

CHARACTERISTICS	MALARIA		OR	95%CI
	Yes (n=58)	No (n=3041)		
Parity				
2+	12	935	1	-
0	28	1246	1.63	0.78 – 3.41
1	18	860	1.75	0.89 – 3.46
Gestation age at first antenatal visit				
2nd and 3rd trimester	29	1640	1	-
1st trimester	29	1401	1.35	0.89 – 2.06
Reported income of family				
High (>Rp300,000)	4	699	1	-
Middle (Rp 200-300,000)	13	826	2.75	0.89 – 8.47
Low (Rp30-200,000)	38	602	11.03	3.91 – 31.08
Maternal education				
Secondary	14	912	1	-
Primary	44	2129	1.35	0.73 – 2.47
Occupation				
Sedentary	6	310	1	-
Manual job	35	1484	1.22	0.50 – 3.57
Housewife	17	1247	0.70	0.26 – 2.20
Husband's education				
Secondary	17	1109	1	-
Primary	41	1932	1.38	0.78 – 2.45
Husband's occupation				
Sedentary	6	527	1	-
Manual job	51	2454	1.46	0.78 – 5.23
None	1	60	1.83	0.03 – 12.37
History of malaria within 6 months before LMP	9	52	10.56	4.57 – 23.72
History of taking chloroquine or SP within 6 months before LMP	8	44	10.90	4.48 – 25.61

LMP=last menstrual period; SP=sulphadoxin-pyrimethamin

In this study low income is classified as a reported income for a family of less than Rp 200,000 per month. Women in malaria parasitaemic group were commonly poorer and had a low education level than those who were free from malaria. In this study, low income is a significant risk predictor for malaria (OR= 11.03; 95%CI: 3.91-31.08). TABLE 2 also shows that maternal education, maternal occupation, husband's education and husband's occupation were not significantly associated with the incidence of malaria.

Women who had reported a history of malaria or history of taking antimalarial drugs 6 months before their last menstrual period (LMP) showed an increased risk of developing malaria during pregnancy (OR= 10.56; 95%CI: 4.57-23.72 and OR = 10.90; 95%CI: 4.48-25.61) respectively.

TABLE 3. Parasite clearance after chloroquine treatment

	No. aparasitaemic/Total cases followed up	
Day	*P. falciparum* (n=30)	*P. vivax* (n=28)
0	30/30	28/28
4	8/30 (26.67%)	11/28 (39.29%)
7	20/30 (66.67%)	20/28 (71.43%)
14	0/30 (100%)	0/28 (100%)
21	0/30 (100%)	0/28 (100%)

Pregnant women who were parasitaemic at the first antenatal visit, or during follow up visit or at delivery were treated using chloroquine and were followed up until 21 days after the first treatment initiated. Thick blood smear were taken serially at days 4, 7, 14 and 21 to check for parasite clearance. On day 4, 8 out of 30 women infected with *P. falciparum* (27%) and 11 out of 28 cases of *P. vivax* infections (39%) became aparasitaemic. On day 7, complete parasite clearance was found in further 12 and 9 women infected by *P.falciparum* and *P. vivax* respectively. On day 14 no women was parasitaemic (TABLE 3). The results indicated chloroquine was effective to eliminate both *P. falciparum* and *P. vivax* in pregnant women. No switch therapy to second line drug (Fansidar®) was given, since at day 14 all women showed no parasitaemia.

DISCUSSION

In all malaria endemic areas the frequency and severity of infection are greater in pregnant women than in the same women before their pregnancy, their non-pregnant counterparts, and adult males.[7] The risk of malaria infection among pregnant women is partly determined by the existing level of immunity, which in turn depends on the intensity and stability of malaria transmission.

Pregnant women in this study were generally young, in a first or second trimester, in their first or second pregnancy and of low education. Short stature, low weight, and anaemia were common in the study population, while malaria occurred only in a few women.

The incidence of malaria among pregnant women in this low transmission area was very low, i.e. only 19/1000, which is much lower than any report elsewhere.[9,10,14-19] However, this incidence is little higher than that reported in India by Sholapurkar *et al.*[20] who found the incidence of malaria during pregnancy was 14/1000. With an exception of women who refused to participate or were referred to the district hospital, who were very few (<0.8%) it is unlikely that this study missed any single malaria case in pregnant women. The best explanation of this low incidence is probably the successful malaria control programme conducted by the Ministry of Health of Indonesia since 1970's in all over part of Java-and Bali islands. However, recent data shows that malaria remained a problem in this area with relatively low transmissions[21-23].

The results of this study show that chloroquine is still effective for both *P. falciparum* and *P. vivax*. While chloroquine remains the antimalarial drug of choice in the country, several reports have appeared recently describing apparent clinical unresponsiveness to chloroquine of some *P. falciparum* infections. The findings of studies conducted between 1990-1995 in all 27 provinces showed that chloroquine resistance *P. falciparum* occurred in 20 provinces when both *in vivo* and *in vitro* tests were carried out. The number of samples derived from the studies might be too small to extrapolate the result into an individual area. However, those

studies have raised an alert to the existing problem in the use of chloroquine to treat malaria infections.

Even though no chloroquine resistance to *P. vivax* was reported in Central Java[24], failure of chloroquine treatment against vivax malaria has recently been reported from several areas of Indonesia, i.e. Irian Jaya[25], Nias island[26], North Sulawesi[27] and highly endemic areas of Nabire, Irian Jaya[28] and West Kalimantan[29]. More extensive spread of chloroquine resistant vivax malaria will have significant implications for malaria control programmes, as well as for treatment and prophylaxis of individual.

Some degrees of Fansidar® resistance were also reported by Tjitra, *et al*[30]. This would make the choice of drug for treatment or chemoprophylaxis more difficult in the future. Moreover, the only safe antimalarial drugs available for pregnant women under government policy are only chloroquine and Fansidar®.

An integrated reproductive-health programme with clear priorities is required to improve the services offered to pregnant women. In this context, malaria in pregnancy is a priority area and a major public health problem, the improved control of which requires better integration into healthcare practices.

CONCLUSION

This study shows that low income, history of malaria within 6 months before LMP and history of taking antimalarial drugs within 6 months before LMP are best predictor for malaria in pregnancy in low endemic area. This study also shows that chloroquine is still effective for treating malaria falciparum in pregnancy in Batealit and Mayong I subdistricts, Jepara.

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