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Maqsood A. Bhatti
Aga Khan University

Muhammad Azharuddin
Aga Khan University

Samreen Bhatti

Muhammad Islam
Aga Khan University

Muhammad Aslam Khan
Aga Khan University

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Malaria and Pregnancy: the perspective in Pakistan

Maqsood A. Bhatti, Muhammad Azharuddin, Samreen Bhatti*, Muhammad Islam, Muhammad Aslam Khan
Department of Medicine, Aga Khan University, *Dow University of Health Sciences, Karachi.

Abstract

Objective: To study the effects of malaria on pregnancy outcome.

Methods: A case control study conducted on patients identified by ICD-9 coding system of the hospital medical records. Demographic and clinical data recorded on standardized data sheet and analyzed using SPSS 11.5 software.

Results: Of the total patients, 67.4% were multigravid and 32.6% were primigravid with 78.6% of patients having platelets <150,000. Mean haemoglobin was 9.4 gm/dl in patients and 12.2 gm/dl in controls. Plasmodium Vivax was accounted for 55.8%, P. Falciparum for 41.9%, and P. Ovale 2.3% of infections. In all, 48.8% of patients received oral Chloroquine, 16.3% oral Quinine, 30.3% intravenous Quinine, 20.9% of patients received combination treatment with IV Clindamycin, and one each patient received oral Artemether or oral halofantrine. Two patients had an abortion. One of the following complications including, threatened abortion, preterm labour, ARDS or Cerebral malaria, was observed in one patient each. Mean weight of babies born to cases was 2.8 kg (range 1.4-3.8) and of control babies was 3.2 kg (range 2.5-4.0 kg). No congenital malformations were reported.

Conclusion: Plasmodium falciparum sp, moderate parasitic load, haemoglobin < 10 gm / dL, platelet count < 50,000 / mm^3 and IV quinine with loading dose of 20 mg / kg are identified as few of the potential risk factors for poor outcome in pregnancy (JPMA 57:15;2007).

Introduction

Malaria is hyperendemic in Pakistan, with the majority of infections caused by Plasmodium vivax, although infections with Plasmodium falciparum are increasing and account for about 35--40% of cases.[1] Malaria in pregnant women is widely evaluated in sub-Saharan Africa, where 90% of global burden of malaria and deaths from disease occur.[2] Various studies have shown that pregnant women in endemic areas are highly susceptible to malaria and both the frequency and the severity of the disease is higher in pregnant than non-pregnant women.[3-5] This higher susceptibility has been hypothesized to be due to transient depression of cell mediated immunity which improves with delivery of neonate and decreases with number of subsequent pregnancies.[6] It is also known that parasite density and prevalence of anaemia are highest among primary gravida and decreases with subsequent pregnancy and hence complication rates are higher in primary gravida as compared to multi-gravida patients.[5,7-8] Malaria in pregnancy is significantly associated with higher mortality and morbidity including, cerebral malaria, maternal anaemia, intrauterine growth retardation, premature labour, stillbirth and abortion.[5,9] In addition; drugs used for treatment of malaria can also contribute significantly to complications associated with this disease.

Pakistan is an endemic country for malaria. We present here the data of a case control study on malaria during pregnancy done in a tertiary care hospital of Pakistan.

Patients and Methods

A retrospective case control study was conducted at Aga Khan University Hospital (AKUH), Karachi. AKUH is a 502 bedded private, tertiary care, academic teaching hospital that primarily serves the residents of Karachi (population ~ 8-12 million) and the surrounding Sindh province.

Patients included in the study were adult (age > 15 years) pregnant women diagnosed with malaria, admitted at AKUH between January 1999 to December 2003. Women with malaria during peripartum period were excluded.

Controls were randomly selected from pregnant patients without malaria who were admitted for routine delivery at Aga khan University Hospital in the period of the study.

Three different kinds of variables were recorded on data sheet. These included demographic variables, severity related variables (parasite species, parasite load, supportive lab values, length of hospital stay, pregnancy and malaria related complications, maternal and foetal mortality etc), and miscellaneous variables (parity, week of pregnancy, week of delivery, Apgar score, baby weight etc)

Definitions: Maternal anaemia was defined as haemoglobin < 11 g / dL, low birth weight as weight < 2500 g, preterm labour was delivery before completing 37 weeks of pregnancy, and abortion (miscarriage) as complete expulsion of product of conception before completing 28 weeks of gestation. Intrauterine growth retardation was labeled as per

physician assessment. Parasite load was defined as scanty if load was 1-10 parasites / high power (100) oil immersion field (hpf), moderate if load was 11-100 / hpf, and heavy if it was > 100 / hpf.

Selection of treatment regimen was based on individual physician's assessment and choice.

Statistical Analysis: Patients were identified according to ICD - 9 - CM codes (647.4 & 650). Pregnant patients admitted with malaria were taken as cases and pregnant patients without malaria were taken as control. Data was recorded on standardized data sheet and analyzed on SPSS 11.5 software. The descriptive analysis was done for demographic and clinical features. Results are expressed as mean ± standard deviation for continuous variables and number (percentage) for categorical variables. Univariate analysis was performed by using the Independent Sample t-test corresponding to difference of means and Pearson Chi-square or Fisher's exact test corresponding to proportion whenever appropriate. Odds ratio (OR) and 95% CI (Confidence Interval) were estimated to identify the strength of association with independent factors. P-value < 0.05 was considered as statistically significant and all p-values are two sided. Multivariate analysis was not done due to small total number of cases.

Results

A total of 43 pregnant patients were identified with malaria and 43 pregnant women without malaria were taken as control. Mean age of cases was 26.9 ± 4.7 (range 18-38) years and in control patient was 25.5 ± 4.5 (range 19- 40) years. Only 14 (32.6%) were primary gravida, and 29 (67.4%) were multigravida (Table 1). Twenty four (55.8%) patients presented in 3rd trimester, 11 (25.6%) in second trimester and 8 (18.6%) presented in 1st trimester of pregnancy. P. Vivax accounted for 55.8% P. Falciparum for 41.9

Table 1. Case control comparison of different variables.

Factors	Cases (n=43)	Baby (n=22)	Control (n=43)	Baby (n=43)	P--value
Age (in years)	26.9 ± 4.7		25.5 ± 4.5		0.165
Gravida					
Primary	14 (32.6%)		11 (25.6%)		0.476
Multi	29 (67.4%)		32 (74.4%)		
Apgar Score					
1 minute	7.4 ± 1.0		7.8 ± 0.7		0.084
5 minutes	8.7 ± 0.9		8.9 ± 0.6		0.285
Baby Weight (in kg)	2.8 ± 0.7		3.2 ± 0.3		0.016
Baby Weight < 2500 gms	7 (318%)		-		-
Mother Hemoglobin (g / dL)	9.4 ± 1.6		12.2 ± 0.8		< 0.001

Results are presented as mean ± standard deviation and number (percentages).

Table 2. Malaria associated complications[1] with different risk factors.

Factors	Complication n (%)	No-Complication n (%)	P--value	OR (95% C.I)
Gravida				
* Multi gravida	8 (89)	21 (62)		4.9 (0.5--44.3)
* Primary gravida	1 (11)	13 (38)	0.231	†1
Platelets				
* < 50,000	4 (44)	2 (6)		12.4 (1.8--88.6)
* ≥ 50,000	5 (56)	31 (94)	0.013	†1
Parasite sp.				
* Falciparum	7 (78)	11 (32)		7.3 (1.3--41.2)
* Vivax / ovale	2 (22)	23 (68)	0.023	†1
Parasite load				
* Scanty	4 (44)	14 (41)		1.1 (0.3--5.0)
* Moderate	5 (56)	20 (59)	0.999	†1
Quinine with loading dose				
* Given	3 (33)	3 (9)		5.2 (0.8--32.0)
* Not given	6 (67)	31 (91)	0.095	†1

† Reference category
OR = Odds ratio
C.I = Confidence interval
1. Complications include: Abortion, preterm labor, low birth weight baby, intrauterine growth retardation, ARDS, cerebral malaria

Table 3. Complication rates in primary vs. multi-gravida patient.

Factors	Primi Gravida n (%)	Multi-Gravida n (%)	P--value
Platelets (per mm3)			
* < 50,000	2 (14)	4 (14)	
* ≥ 50,000	12 (86)	25 (86)	0.999
Haemoglobin (g / dL)	10.9 ± 2.0	10.8 ± 1.9	0.784
Baby weight (in kg)			
* < 2.5	2 (11)	5 (11)	
* ≥ 2.5	17 (89)	41 (89)	0.999
Abortion			
* Yes	1 (4)	1 (2)	
* No	24(96)	60 (98)	0.499

Results are presented as mean ± standard deviation and number (percentages).

%, and P. Ovale for 2.3% of infections. Twenty four (55.8%) patients had moderate, 18 (41.9%) had scanty and 1 (2.3%) had heavy parasitic load. Fever was present in 43 (100%) patients while nausea and vomiting in 20 (46.5%) and myalgia in 10 (23.3%) patients. Mean haemoglobin was 9.4 ± 1.6 gm / dL (range 5.4 - 12.8 mg / dL) in cases and 12.2 ± 0.8 g / dL (range 11.0 - 14.4 mg / dL) in controls (P-value <0.001). Six (14%) patients had haemoglobin in the range of 5-7.9 mg / dL (Table 2). Thirty three (78.6%) patients had platelets < 150,000 / mm^3, among them 6 (14%) patients

had platelets < 50,000 / mm^3. The mean length of hospital stay was 4.1 ± 1.7 days (range 1-8 days).

Twenty one (48.8%) patients were treated with oral Chloroquine, 7 (16.3%) with oral Quinine, 7 (16.3%) received intravenous (IV) Quinine with loading dose of 20 mg / kg,6 (14%) received IV Quinine without loading dose, 9 (20.9%) had combination treatment with IV Clindamycin, and one patient each received oral Artemether or oral halofantrine. All patients with falciparum malaria were treated with IV or oral Quinine with or without combination with clindamycin except one who was treated with oral chloroquin and one with oral halofantrine. Most of the patient with vivax malaria were given chloroquin except two, of whom one each received quinine and artemether. Drug regimen selection was based on individual physician's choice.

Twenty two out of 43 patients had babies born in AKUH. Total number of babies in cases were lower because some pregnant patients who were admitted in our hospital for malaria, delivered their babies elsewhere and hence remained unaccounted in our records. Mean weight of babies in cases was 2.8 ± 0.7 kg (range 1.4-3.8 kg) and 3.2 ± 0.3 kg (range 2.5- 4.0 kg) in control babies (P=0.016). Seven babies were delivered with preterm labour, all were < 2.5 kg in weight. Two patients had an abortion, one was primary gravida and the other multigravida. One of the following complications including, threatened abortion, ARDS, Cerebral malaria, and recurrence of falciparum malaria was observed in one patient each. Recurrence of P. falciparum was seen in a patient whose first episode was treated with oral chloroquine. Specific risk factors including parasite sp, parasite load, gravidity, thrombocytopenia and IV quinine loading dose were identified in patients with pregnancy and malaria associated complications (Table 2).

No congenital malformations in babies were reported in charts except for one baby who was diagnosed with Potters syndrome and died at age of 4 days, her mother was suffering from polycystic kidney disease. This patient received IV quinine without loading dose in combination with IV Clindamycin during 14th week of pregnancy for Falciparum malaria.

Total seven patients received IV Quinine with loading dose and two of them developed complete abortion during treatment. Both patients had Falciparum sp. with moderate parasitic load and platelet count of < 50,000 / mm^3. One pregnant patient died in third trimester with Adult respiratory distress syndrome secondary to severe malaria.

Discussion

Malaria poses a serious health problem to pregnant women. We have described important epidemiologic features and clinical characteristics of 43 patients who had malaria during pregnancy and compared some of the important complications with control pregnant patients without malaria.

In Pakistan, majority of infections in pregnant patients are with P. Vivax sp., but complications of malaria are mostly seen in P. falciparum sp. The incidence of severity of infection and pregnancy related complications varies according to level of acquired immunity against infections and the parity.[10] In this study, the susceptibility to malaria infection was high in multi-gravida compared to primigravida patients but associated complications were not statistically significant in both groups. This is in contrast to various studies published from Indian subcontinent where complication rate was higher in primary gravida compared to multigravida patients.[5,11,12] Falciparum malaria, moderate parasitic load, haemoglobin < 10 mg / dL, platelet count < 50,000 / mm^3, and use of IV quinine with loading dose of 20 mg / kg were identified as few of the potential risk factors for poor outcome of pregnancy.

In highly endemic areas the peak level of falciparum parasitemia occurs between 9 to 16 weeks of gestation and then decreases progressively until delivery.[5] In our study 55.8% of patients presented in third trimester of pregnancy, this is in contrast to previously reported higher incidence in second trimester of pregnancy.[5]

One out of 43 patients died during hospitalization due to underlying severe malaria and ARDS. She presented in 30th week of pregnancy with scanty parasitic load of falciparum sp., haemoglobin was 8.5 gm / dl and platelet count of 45000 / mm^3. The mortality rate in our patients was much lower than previously reported figures from other countries.[5,12,13] Kochar et al associated significant anaemia (Hb. 5 g%) as the prime cause of mortality in his cohort of patients. In our patients malaria was significantly associated with haemoglobin decline of at least 2.8 gm compared to control group (P < 0.001), but it was not associated with a higher mortality rate. The reason could be that in our group, the severity of anaemia was much lower compared to the cohort in Kochar's study with higher mortality.[5]

Placental malaria is a significant cause of pregnancy related complications in the form of low birth weight babies, preterm deliveries, still birth and abortion.[5] In our study, 7 pregnant patients had preterm live birth and all of those babies were less than 2500 gm in weight. Overall there was 400 gm decrease in birth weight of babies born to pregnant women with malaria compared to pregnant patient without malaria (P = 0.016). The biologic mechanism by which placental malaria infection leads to low birth weight is not fully established. P. falciparum infected placenta

shows thickening of basement membrane of placental trophoblast cells, potentially resulting in reduced nutrient transfer to the foetus.[14] Placental microinfarcts have been reported; transplacental passage of parasitized RBC to foetus does occur, and this may affect foetal nutrient use or stimulate preterm labour.[14]

Limited data are available regarding spontaneous abortion as a complication of clinical malaria or associated anti-malarial drugs in therapeutic doses. In our study seven patients received intravenous quinine with loading dose of 20 mg / kg body weight. Two of these patients aborted. One was admitted with history of vaginal bleeding prior to treatment with quinine. The patients with abortion had some common features like, falciparum malaria with moderate parasitic load, haemoglobin < 10g/dL and platelet count of < 50,000 / mm^3 and both patients received IV quinine with loading dose. Various authors from other parts of the world have reported that malaria is not an important cause of spontaneous abortion in highly endemic areas.[4,5,11] Although both of our patients had severe malaria; in one of the them the loading dose of quinine might have precipitated complete abortion from threatened abortion.

Malaria has been a known cause of increased neonatal mortality.[12] In the present study no significant foetal mortality was observed among pregnant patients with malaria compared to pregnant women without malaria except for one baby who died due to Potters Syndrome whose mother had a history of polycystic kidney disease.

One of the important limitations of our study was the selection of patients. Since our hospital is a tertiary care private hospital, people belonging to the lower socioeconomic class where malaria is more endemic, could not have an easy access due to the cost factor. Hence the patient population studied cannot truly represent the general population of Pakistan.

Conclusion

In our country malaria is more common in multigravida and third trimester of pregnancy. It is significantly associated with decreased maternal haemoglobin and low birth weight of newborn. P. falciparum sp, moderate parasitic load, hb < 10 g/dL, platelet count < 50,000 / mm^3, and IV quinine with loading dose of 20 mg / kg are identified as few of the potential risk factors for poor outcome in pregnancy.

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