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Original Article

Obstetrics and Gynaecology Section

Comparative Study on Antenatal and Perinatal Outcome of Vivax and Falciparum Malaria in a Tertiary Care Hospital of Kolkata, India

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ABSTRACT

Introduction: Malaria occurring in pregnancy is associated with considerable maternal and perinatal morbidity. In India, the problem is compounded by dual parasitological aetiology of *Plasmodium vivax* (*P. vivax*) and *Plasmodium falciparum* (*P. falciparum*).

Aim: To compare the outcome of infections by *P. vivax* and *P. falciparum* species among pregnant women in a hospital setting.

Materials and Methods: Pregnant women who tested positive for malaria either by microscopy of peripheral blood smear or ELISA test for double antigen were enrolled in the study. They were followed up till their delivery and discharge from hospital. Demographic, clinical and laboratory data was collected at enrolment, on event of complication and at delivery. Data was analyzed for univariate and multivariate associations.

Results: There were 64 pregnant women diagnosed with malaria. A total of 76.6% study subjects had vivax infection rest was infected with *p. falciparum*. Anaemia (84%) was the commonest complication. A total of 60.9% women had pathological placenta. Preterm delivery, low birth weight and Apgar score <7 were the adverse pregnancy outcomes which were more frequent with falciparum infection. There were three perinatal deaths. Multigravidas were at significantly higher risk for low birth weight and low Apgar score of newborn. Infection in later trimester was associated with low Apgar score.

Conclusion: Both types of malaria cause considerable morbidity in pregnant women. More cases occurred among primigravida but multigravida and later trimester of pregnancy had more severe disease.

Keywords: Malaria epidemiology, Malaria falciparum, Malaria vivax, Malaria control, Pregnancy complications, Parasitic, Malaria pigment, Anaemia, Apgar score

INTRODUCTION

Malaria is an infection caused by several species of the protozoa plasmodium spicies Human infections occurs by bite of infected female Anopheles mosquitoes. The disease spectrum ranges from asymptomatic infections, febrile illness to severe disease like cerebral malaria. The disease has many epidemiological forms depending on vector type, parasite type and level of prevalence. Malaria infection in pregnancy (PM) is an important cause of maternal and perinatal morbidity and mortality in malaria endemic regions. The clinical presentation depends on the intensity of transmission and immunity of pregnant women to malaria. In regions of low (unstable) transmission PM may cause maternal and foetal death, neonatal death and Low Birth Weight (LBW). Severe disease occurs due to lower immunity. In areas of stable malaria transmission higher number of cases of PM will occur but it can be associated with asymptomatic infection and placental parasitaemia [1,2]. Parasite isolated from placenta is suggestive of acute malaria whereas in chronic case malaria pigment is deposited in placenta. Histopathological examination of affected placenta shows sequestration of parasite along placental membrane, villous hypertrophy, fibrinoid necrosis of villi and deposition of malarial pigment. Adverse outcomes like LBW, anaemia in pregnancy and high infant mortality also occur [1]. India is trapped within the triad of high population, high fertility and high malaria transmission. Every year large number of cases of PM occurs in India. Two major parasite species are *P. falciparum* and *P. vivax*. In a study conducted in Jabalpur, Central India, the Slide Positivity Rate (SPR) for malaria parasite was 17% for antenatal women in contrast to 8% among febrile non-pregnant women. Pregnant women also had significantly higher mean parasite density compared to non pregnant women for both parasitological types of malaria [3]. Current knowledge on PM is acquired from studies conducted in Africa with emphasis on falciparum infection. The pathophysiological effect of *P. vivax* in pregnancy is less clear. Malaria and pregnancy being mutually aggravating factors, there is need to understand the effect of PM with its dual aetiology of vivax and falciparum infection in India. Present study was planned to document the effect of PM in an endemic setting. We conducted the study at a tertiary level medical college hospital of Kolkata. In the city of Kolkata malaria transmission in perennial, but more cases occur in the monsoon and post monsoon seasons of July to December coinciding with the increase in vector density. Peak incidence for *P. vivax* malaria is in September while that of *P. falciparum* malaria is in November [4]. So we collected data for an entire year to accommodate for the seasonal variation. The aim of our study was to detect malaria infection among febrile antenatal women along with parasitological diagnosis, follow up for outcomes and analysis of observed factors responsible for adverse perinatal outcomes.

MATERIALS AND METHODS

The present study was a prospective hospital based epidemiological study. The period of study was from February 2014 to November 2015. The study was conducted in the gynaecology and obstetrics department of a tertiary level government medical college hospital of Kolkata, India, providing specialty and super specialty health care services.

This study was approved by Institutional Ethics Committee of

Age and Obstetric status		Parasitological type of malaria		Total women (n=64) No (%)
		P. vivax (n=49) No (%)	*P. falciparum* (n=15) No (%)	
Age (in years)	≤ 23	23 (46.9)	10 (66.7)	33 (51.6)
	24-35	26 (53.1)	5 (33.3)	31 (48.4)
Gravidity	Primigravida	26 (53.1)	10 (66.7)	36 (56.3)
	Multigravida	23 (46.9)	5 (33.3)	28 (43.8)
Trimester of pregnancy at diagnosis of malaria	First	12 (24.5)	6 (40.0)	18 (28.13)
	Second	36 (73.46)	6 (40.0)	42 (65.62)
	Third	1 (2.04)	3 (20.0)	4 (6.25)

[Table/Fig-1]: Distribution of parasitological type of malaria according to age and obstetric status.

Presence of antenatal and perinatal complications	Parasitological type of malaria		Total subjects (n=64) No(%)
	P.vivax (n=49) No (%)	*P.falciparum* (n=15) No (%)	
Presence of anaemia	39 (79.6)	15 (100.0)	54 (84.4)
Other medical complications	18 (36.7)	13 (86.7)	31 (48.4)
Pathological placenta	26 (53.1)	13 (86.7)	39 (60.9)
Preterm delivery	23 (46.9)	9 (60.0)	32 (50.0)
Low birth weight	38 (77.6)	13 (86.7)	51 (79.7)
Apgar score <7	35 (71.4)	12 (80.0)	47 (73.4)
Perinatal mortality	1 (2.0)	2 (13.3)	3 (4.7)

[Table/Fig-2]: Distribution of study subjects according to malaria type and complications.

Medical College Kolkata. Informed written consent in vernacular was obtained from each participant prior to data collection. Respondents were assured about confidentiality of information and its intended use for academic purpose.

Sampling for the study was purposive. All pregnant women with fever were eligible to participate in the study. Inclusion criterion was diagnosis of malaria. Refusal of consent to participate in the study was only exclusion criteria. Fever was defined as an axillary temperature of ≥101 F. Pregnant women attending antenatal clinic with history of fever in last two days but afebrile at presentation were also eligible. Subjects were enrolled in the study till January 2015. Cut off time for follow up was November 2015. For all eligible women blood was collected by finger prick method. Thin and thick smears were prepared, stained with Giemsa and examined under microscope. Double antigen test for malaria using ELISA rapid kit was also performed. Subjects whose peripheral blood smear showed malaria parasite or were tested positive by rapid antigen kit or both were included for further follow up. All cases of fever were treated according to standard protocol. Out of 183 pregnant women reporting with fever, 64 were diagnosed having malaria and comprised the final study subjects. All 64 women were followed up as outdoor patients till their delivery. They were admitted in event of moderate to severe anaemia, complications and during delivery. Data was collected in a structured schedule at beginning of the study, in event of complication and after delivery. Method of data collection was by interviewing the study subjects, checking of reports and clinical examination. Information was collected on demographics, present and past pregnancies and relevant medical history. General examination, morphometry of uterus and wherever indicated 2D ultrasonography was performed. Newborns were weighed immediately after birth, standard newborn resuscitation measures were practiced and Apgar score was recorded at one minute and five minutes after birth. Placentas from all deliveries were preserved at 2^0C–8^0C and send to the laboratory within two hours for histopathological examination. Response rate was 100% and there was no subject lost to follow up.

Criteria for variables: Haemoglobin% <7 gm/dl was considered severe anaemia, 7-10 gm/dl as moderate anaemia, 10-<11gm/dl as mild anaemia and 11 gm/dl or more as no anaemia. Birth weight <2.5 kg was considered low birth weight and five minute Apgar score <7 was considered as low Apgar score. Placenta showing changes due to deposition of malaria pigment or presence of malaria parasite according to histopathological report was considered to be pathological placenta.

STATISTICAL ANALYSIS

Data were concurrently entered in Microsoft Excel 2007 spread sheet for frequencies and percentages calculation. Statistical Package for Social Sciences software version 16.0 was used for testing association between predictor and outcome variables. Initially statistical associations were tested by univariate analysis followed by multinomial logistic regression for significant associations. A p-value <0.05 was considered as statistically significant.

RESULTS

Total 64 pregnant women participated in this study. Mean age of the respondents was 23.5 years (SD=5.3) with a range between 17 to 35 years. The study population was mainly inhabitants of Kolkata and neighbouring areas. Diagnosis of *P. vivax* infection was considerably higher (76.6%) than *P. falciparum* infection (23.4%). Higher proportion of women for both types of malaria were primigravida and in their second trimester of pregnancy. Overall 43.7% of the subjects were primigravida in their second and third trimesters of pregnancy at the time of diagnosis of malaria. Fifty two (81.2%) women were febrile at the time of admission. Complications were comparatively higher for *P. falciparum* infection. In this study we have considered anaemia and other medical complications independently. All subjects with *P. falciparum* infection had anaemia and majority also had one or more of other medical complications like mild jaundice (39%), hypoglycaemia (29%), diarrhoea (16%), convulsion (7%), deep jaundice (6%) and acute renal failure (3%). Despite of the high overall complication rate for both type of malaria (48.4%) there was no maternal mortality. Overall prevalence of anaemia was very high (84.4%). A total of 40.6% women had moderate to severe anaemia.

Adverse pregnancy outcomes	df	Preterm birth	Birth weight	Apgar score	Perinatal mortality
Parameters		p-value#			
Age: ≤ 23, 24-35	1	0.74	0.44	0.11	0.75
Trimester: First, second, third	2	0.40	0.21	0.04*	0.95
Gravidity: Primi, multi	1	0.10	0.02*	0.03*	0.99
Type of malaria: Vivax, falciparum	1	0.87	0.18	0.81	0.99
Pathological: Placenta, present, absent	1	0.82	0.94	0.89	0.37
Anaemia: No, mild, moderate, severe	3	0.21	0.14	0.31	0.03*
Complications: Present, absent	1	0.21	0.84	0.20	0.11

[Table/Fig-3]: Association of adverse pregnancy outcomes with age, type of malaria, obstetric status and complications (n=64).
* Statistically significant. # by chi-square test

Parameters	B	Std error	Exp(B)/ AOR#	95% C.I. of Exp(B)	Sig
Apgar score					
Trimester (df=2)					
First trimester	-3.67	1.64	0.02	0.001-0.63	0.02*
Second trimester	-3.44	1.60	0.03	0.001-0.73	0.03*
Third trimester	Ref				
Gravidity (df=1)					
Primigravida	-1.6	0.81	0.2	0.04-0.97	0.04*
Multi gravida	Ref				
Birth weight					
Gravidity (df=1)					
Primigravida	-1.77	0.82	0.17	0.03-0.85	0.03*
Multi gravida	Ref				
Perinatal mortality					
Severity of anaemia (df=3)					
Absent	-35.28	0.00	<0.0001	-	-
Mild	-35.59	7833.7	<0.0001	-	-
Moderate	-35.46	1.091E4	<0.0001	-	-
Severe	Ref				

[Table/Fig-4]: Parameter estimates of statistically significant variables for pregnancy outcome.
AOR= adjusted odds ratio; * Statistically significant; Exp(B)-This is the exponentiation of the B coefficient

A total of 46.8% of pregnant women had malaria with one or more medical complication. Pathological placenta was a common finding (60.9%). Half of the participants had preterm delivery and even higher proportion delivered a baby with birth weight <2.5 kg. All the deliveries were singleton and the mean birth weight of the newborns was 2.3 kg (SD=0.4). Low Apgar score i.e., seven or less was recorded for >70% of neonates at five minutes after birth. There was 4.7% perinatal mortality [Table/Fig-1]. Preterm delivery, low Apgar score, low birth weight of the newborns and perinatal death were considered as adverse pregnancy outcomes.

Univariate analysis by chi-square test was done to check for the associations between age, obstetric status of the subjects, type of malaria and its complications with adverse pregnancy outcomes. Significant statistical associations were present between Apgar score with pregnancy trimester at diagnosis of malaria and gravidity status of the subject. Other significant associations were gravidity status with birth weight and anaemia with perinatal mortality [Table/Fig-2]. Response variables were binomial except for pregnancy trimester (first, second and third) and anaemia (absent, mild, moderate and severe), so multinomial logistic regression was used for parameter estimation of the predictor variables which showed significant association by univariate analysis. [Table/Fig-3] shows parameters of the predictor variables which were significantly associated with adverse pregnancy outcome. Adjusted odds ratio of risk was compared with reference category. Risk of <7 Apgar score at five minutes after birth was higher for women who had malaria in their third trimester of pregnancy. This risk was also higher for multigravid subjects. Multigravid women also had higher risk of delivering baby with birth weight <2.5 kg. Risk of perinatal mortality was higher for severe anaemia [Table/Fig-4].

DISCUSSION

With lack of longitudinal studies on PM in India, our study should be of special interest. Most studies in India on PM were conducted in the malaria endemic states of Chattisgarh, Madhya Pradesh and Jharkhand of Central and Eastern region with predominantly tribal population. These regions have higher prevalence of *P. falciparum* infection [3,5].

In the Chattisgarh study, prevalence of *P. vivax* among pregnant women was 33% and *P. falciparum* was 67% [3]. In another cross-sectional study, conducted at the state of Jharkhand *P. falciparum* was 53%, *P. vivax* 37% and 10% mixed infection [6]. In our study, *P. vivax* was more prevalent (76.6%). Differential geoparasitological distribution is probably responsible for this finding.

At present *P. falciparum* contributes >60% of total malaria burden of India, more cases are seen among tribal populations living in the forested areas of Jharkhand, Chattisgarh and Odisha [7]. In West Bengal *P. falciparum* contributes for only 16% of cases [7]. It is hypothesized, pathological effects of *P. vivax* in PM is mainly due to anaemia, while that of *P. falciparum* is due cytoadhesion in placental intervillous space and triggering off the inflammatory cascade [8].

Placental changes can be seen in vivax malaria as well [9]. Placental pathology is associated with preterm delivery and low birth weight [10]. In our study, there was high proportion of pathological placenta as well as preterm delivery, low birth weight; but there was no statistically significant association between them.

More than 70% of women with *P. vivax* in our study had anaemia and delivered a low birth weight infant. There were also preterm delivery, low Apgar score and one perinatal death.

A case series of 12 subjects with pregnancy associated *P. vivax* is reported from NE Venezuela with complications like anaemia and thrombocytopenia. They also reported adverse pregnancy outcomes as miscarriage and preterm births [11]. In a systematic analysis of Brazilian literature, anaemia was the most common complication and other maternal complications reported were hepatitis, jaundice and hypoglycaemia in PM associated with *P. vivax*, which is in agreement with present study findings [12].

Complications were comparatively more with falciparum malaria in our study which is corroborated with studies from Sub-Saharan Africa [13]. There is negative association with gravidity and susceptibility to malaria in pregnancy [10]. Likewise in our study more women were primigravida and this was more pronounced for falciparum malaria. However, adverse pregnancy outcome was higher for multigravida. There were more cases in first and second trimesters of pregnancy and only few in third trimester. But low Apgar score in newborn was statistically associated with malaria infection in later trimesters.

It can be hypothesized from our study and literature reviews that immunity against malaria infection increases with number and duration of pregnancy. Non immune or partially immune women get infections at later trimester or with higher order of pregnancy, hence they have more severe disease [10]. The statistical result however should be interpreted keeping in view the lower number of subjects with falciparum malaria and the covariability existing between the predictor variables. There is covariability between birth weight and Apgar score. Anaemia in pregnancy is a major confounding variable which is associated with pregnant state itself, can be an independent predictor of adverse pregnancy outcomes like preterm birth, low birth weight and also associated with malaria and its complications [14-16]. Similarly, there is covariability between preterm birth, low birth weight and low Apgar score.

In this study we found, though number of cases were higher for primigravida women and lower duration of gestation, adverse outcome were lower for this group. More cases in earlier trimesters and among primigravida can be explained by the immunological phenomenon of blocking antibodies. Plasma antibodies against falciparum encoded Variant Surface Antigens (VSA), expressed on the surface of infected erythrocytes blocks cytoadhesion of the parasite to placental chondroitin sulphate A. Such blocking antibodies offer protection against PM. The titer of Anti VSA antibody increases with subsequent pregnancies and probably also with duration of gestation [17-19]. It is however not known whether similar immunological phenomenon happens in *P. vivax*. There is also knowledge gap in relation of timing of infection with respect to

period of gestation and its role on placental development and fetal organogenesis.

Host immune response to malaria is considered as an important determinant of clinical manifestation of disease. The immune picture is further complicated by superimposed pregnancy. We did not explore the immunology of malaria in our study.

LIMITATION

The study results are limited by this lack of information on individual immune responses [20-22]. We also did not follow up the women and their newborns for any long term sequelae of malaria.

CONCLUSION

So far the focus of medical research has been mostly on *P. falciparum*, in Sub-Saharan Africa. The observation that *P. vivax* can also cause severe disease in pregnancy has resulted in renewed interest in research on vivax malaria in unstable malaria transmission areas. Pregnancy associated malaria occurs in higher frequency among paucipara women in early trimesters of pregnancy living in endemic areas. However, infected multipara women have higher risk of adverse pregnancy outcome. Research into the immunology associated with *P. vivax* and also for better management decisions in pregnancy with malaria is necessary to further improve maternal and child health.

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