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# Predictors of asymptomatic malaria in pregnancy

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**Summary:** A number of studies have described malaria parasitaemia in pregnancy as mostly an asymptomatic condition, however information about predictors of asymptomatic malaria is largely lacking. We investigated the prevalence of symptoms and potential predictors of asymptomatic malaria in pregnant women attending Ante-Natal Clinic (ANC) of two public maternity hospitals in Ibadan, Southwest-Nigeria. Demographic data, history of previous and present pregnancy were obtained from the subjects and blood smears were examined for malaria diagnosis by light microscopy. Seventy – seven parasitaemic pregnant women attending antenatal clinic were evaluated for presence or absence of symptoms that may be associated with malaria. Thirty-seven women (48%) were asymptomatic whereas 40 (52%) presented with symptoms such as weakness, headache and general body ache and fever. Parasite density was significantly higher in symptomatic patients (P = 0.042), while asymptomatic patients had low level parasitaemia but significantly higher gametocyte carriage (P = 0.035). In conclusion, parasitaemic pregnant women resident in hyper- or holo-endemic malaria region are likely to be symptomatic with increasing density of the parasitaemia.

**Keywords***:* Malaria, Pregnancy, Asymptomatic, Parasitaemia, Women



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## INTRODUCTION

Malaria remains a major health challenge globally (Guerin *et al*., 2002) especially in children under five, pregnant women and non-immune visitors to malaria endemic regions. Nigeria accounts for about a quarter of all malaria cases in the 45 malaria-endemic countries in Africa (WHO, 2008). The susceptibility of pregnant women to malaria was first attributed to reduced cellular immunity to *Plasmodium falciparum* antigens (Riley *et al*. 1989) and recently linked to the level of antibodies to placental sequestrated parasites (Elliott *et al*., 2005). The principal impact of malaria infection is due to the presence of parasites in the placenta causing maternal anemia (Newman *et al*., 2003; Guyatt and Snow, 2004; Rogerson and Boeuf, 2007), low birth weight (LBW) and infants death (Steketee *et al*, 1996).

*Plasmodium falciparum* associated maternal mortality remains unacceptably high (Brabin and Verhoeff, 2004) and in Nigeria, maternal mortality attributable to malaria is reported to be about 11% (Fed. Min. Hlth., 2000). WHO recommends the use of sulphadoxine-pyrimethamine as intermittent preventive treatment during the second and third trimesters as well as Insecticide Treated Nets by pregnant women in endemic Africa (Guyatt and Snow, 2004; Rogerson and Boeuf, 2007). Both preventive modalities have been adopted by most sub-Saharan African countries although coverage remains poor.

Reports suggest that most cases of malaria in pregnancy in areas of stable malaria transmission are asymptomatic (Anorlu *et al*., 2001; Mockenhaupt *et al*., 2002). This study attempts to explore malaria associated symptoms and predictors of asymptomatic malaria in pregnant women with peripheral parasitaemia.

## MATERIALS AND METHODS

### *Study location*

The study was conducted at Aremo Maternity Centre (centre I) and Adeoyo Maternity Hospital, (centre II) both of which are located in the central part of Ibadan, south-western Nigeria and are public owned facilities.

***Enrolment and Conduct***

This non-interventional study of malaria parasitaemia and malaria-associated symptoms was approved by (AD13/262/184) the Research and Ethical Committee of the Ministry of Health, Ibadan Oyo State, Nigeria as part of a larger study of malaria epidemiology and chemotherapy in pregnancy.

Blood film positivity for malaria, clinical and ultrasound evidence of pregnancy and consent to participate were the inclusion criteria for entry into the study. Each participant was subsequently interviewed with respect to obstetric history and malaria preventive measures, antimalarial drug use in the preceding 1 month as well as presence or absence of any symptoms. General physical and obstetric examinations were carried out by midwives and two of the investigators (FAF and OAA) and heamatocrit determined thereafter. Trimester was defined as first trimester (<14 weeks), second trimester (14—27 weeks) and third trimester (>27 weeks).

***Detection and quantification of malaria parasite***

Thin and thick blood smears were Giemsa-stained and evaluated using Light Microscope at X100 objective magnification. Speciation and quantification of *Plasmodium falciparum* asexual and sexual stages were carried out according to standard WHO protocols (WHO, 2005). Briefly, parasite quantification were evaluated on thick blood smears and based on the number of white blood cells corresponding to 500 asexual stage of parasite or the number of parasites found by counting a minimum of 500 white blood cells whichever occurred first. Parasites density was estimated assuming white blood cell count of 8000 /µL of blood (Trape, 1985). All the study slides were initially evaluated by any two experienced microscopists (AAA, STB and FAF) independently and the average of their results taken.

***Statistical Analysis***

Data were double entered using EpiData version 3 (Lauritsen, 2008) and analyzed using SPSS version 15.0 (SPSS Inc., USA). Proportions were compared using $\chi^2$ with Yates' correction or Fisher exact tests. Normally distributed, continuous data were compared by Student's t-tests and analysis of variance (ANOVA). Data not conforming to a normal distribution were compared by the Mann-Whitney U-tests and the Kruskal-Wallis tests. A univariate analysis and multivariate logistic regression models were used to determine the factors associated with asymptomatic infection. P-values of $\leq 0.05$ were taken as statistically significant.

## RESULTS

***Subjects characteristics and malaria-associated symptoms at enrolment***

Approximately, 52, 23 and 25% of the parasitaemic subjects were *primigravidae, secundigravidae* and *multigravidae*, respectively while 5, 52 and 43% were in the first, second and third trimesters, respectively. The characteristics of the symptomatic and asymptomatic parasitaemic subjects are presented in Table 1. Symptoms including weakness, body aches, headache and fever were documented in 40 of 77 (52%) parasitaemic subjects. The most common symptom reported among the 40 symptomatic women was weakness, being the sole presenting symptom or one of the symptoms in 68% of the cases. It is noteworthy that only 5 (13%) of the symptomatic individuals presented with fever (Figure 1).

***Malaria parasitaemia in pregnancy***

The overall geometric mean (range) parasite density was 1887 (40–30 901) and was significantly higher in symptomatic than asymptomatic subjects (2909 (40–30 901) *vs* 783 (40–8 829), P = 0.04). The geometric means (range) parasite density of participants at first, second and third trimesters were 1798 (80-5024) (n = 4), 1466 (30-30901) (n = 40) and 2408 (40-15333) (n

**Table 1:**
Demographic and clinical characteristics of 77 pregnant women with peripheral parasitaemia

| Parameters | Asymptomatic | Symptomatic | Total | *P value |
|---|---|---|---|---|
| Number | 37 | 40 | 77 | – |
| Age (years) | 25.4 ± 5.1 (15.0 – 35.0) | 25.7 ± 5.1 (18.0 – 40.0) | 25.5 ± 5.1 (15.0 – 40.0) | 0.65 |
| PCV (%) | 30.8 ± 3.9 (22.0 – 40.0) | 30.2 ± 3.1 (25.0 – 36.0) | 30.4 ± 3.5 (22.0 – 40.0) | 0.42 |
| No with PCV < 30 % | 16 | 19 | 35 | 0.69 |
| Gestation age at booking (weeks) | 23.7 ± 6.3 (8.0 – 36.0) | 23.7 ± 6.1 (8.0 – 36.0) | 23.7 ± 6.2 (8.0 – 36.0) | 0.96 |
| Parity | 0.7 ± 0.1 (0.0 – 3.0) | 0.9 ± 0.2 (0.0 – 4.0) | 0.8 ± 0.1 (0.0 – 4.0) | 0.23 |

*Compared asymptomatic and symptomatic subjects

**Table 2:**
Determinants of asymptomatic infection in pregnant women with uncomplicated falciparum malaria

| Variables | Number | | Crude odd ratio (95% CI) | P value | Adjusted odd ratio (95% CI) | P value |
|---|---|---|---|---|---|---|
| | Enrolled | AM | | | | |
| GA(weeks) | | | | | | |
| First | 4 | 0 | 1 | | 1 | |
| Second | 40 | 17 | 1.63 (0.19 – 14.19) | 0.147 | – | – |
| Third | 33 | 20 | 2.71 (0.33 – 22.00) | **0.036** | *1.68* | 0.09 |
| Parity | | | | | | |
| Primigravid | 40 | 20 | 1 | | | |
| Secondigravid | 19 | 9 | 0.90 (0.61 – 1.33) | 0.85 | – | – |
| Multigravid | 18 | 8 | 0.80 (0.52 – 1.23) | 0.78 | – | – |
| PCV (%) | | | | | | |
| < 30 | 35 | 16 | 1 | | | |
| ≥ 30 | 42 | 21 | 1.19 (1.09 – 1.29) | 0.82 | – | – |
| Previous ANC | | | | | | |
| No | 68 | 30 | 1 | | 1 | |
| Yes | 9 | 7 | 4.40 (1.17 – 16.85) | **0.048** | 4.85 (0.90 – 26.3) | 0.066 |
| Parasitaemia | | | | | | |
| < 2000 | 67 | 36 | 1 | | 1 | |
| ≥ 2000 | 10 | 2 | 0.22 (0.06 – 0.80) | **0.042** | 0.19 (0.04 – 1.04) | **0.049** |

ANC=Ante-natal care, AM=Asymptomatic malaria parasitaemia, GA= Gestation age, PCV=Packed cell volume, IPT= Intermittent Preventive Treatment

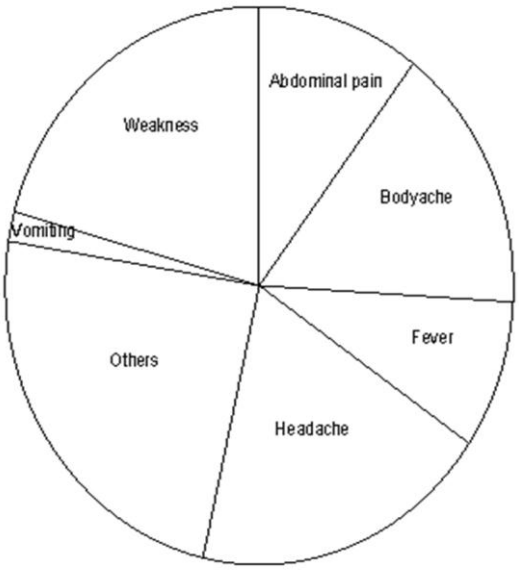



Figure 1. Prevalence of symptoms in pregnant women with peripheral parasitaemia

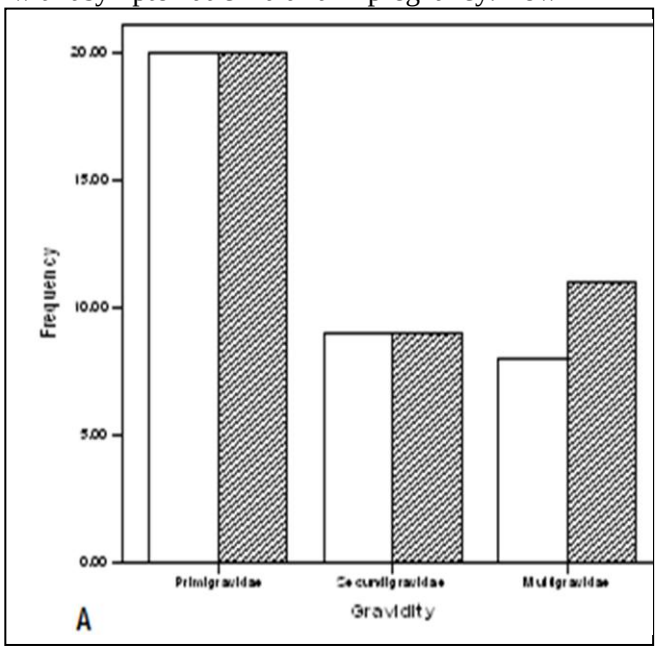
= 33); (P = 0.695). The proportion of subjects who had parasite density ≥ 2000 asexual parasites/µL of blood was significantly higher in symptomatic (23%) than asymptomatic (5%) subjects ($\chi^2$ = 13.46; df = 1; P = 0.00024). Of the 77 subjects with patent parasitaemia, 10 (13%) had patent gametocytaemia with significantly higher proportion in asymptomatic (7/37) (18%) than symptomatic (3/40) (8%) subjects ($\chi^2$ = 4.42; df = 1; P = 0.035). The overall geometric mean (range) gametocyte density was 49 (8–264) gametocytes /µL and was similar in both asymptomatic (26 (8–64) gametocytes/µL) and symptomatic groups (101 (8–264) sexual parasites/µL) (P = 0.17). Figure 2 shows the distribution of malaria parasitaemia associated with or without symptoms.

The distribution of symptomatic or asymptomatic parataemia was similar among various sub-populations of the participants, thus the proportion of *primigravidae*, *secundigravidae* and *multigravidae*with symptomatic parasitaemia were: 20/40 (50%), 9/18 (50%) and 11/19 (58%), respectively ($\chi^2$ = 1.72; df = 2; P = 0.42) (Figure 2). Symptomatic malaria parasiatemia was significantly least prevalent in subjects during third trimester (14/34, 41%) than first (2/3, 67%) and second (24/40, 60%) trimesters ($\chi^2$ = 14.69; df = 2; P = 0.00065). Symptomatic malaria parasitaemia were more frequently observed during the booking visit and if gestation at booking was < 25 weeks; (55.9%, OR (95% CI): 2.5 (1.9 – 3.1), P = 0.0000008 and 67.5%, OR (95% CI): 2.8 (2.6 – 3.2), P = 0.0000004).

***Determinants of asymptomatic malaria in pregnancy***

The proportion of asymptomatic subjects in third trimester (20/34, 59%) of the gestation is significantly higher than those in first (1/3, 33%) and second (16/40, 40%) trimesters ($\chi^2$ = 14.69; df = 2; P = 0.00065); the relative risk of asymptomatic malaria occurring during the third trimester was significantly

higher than first and second trimesters (RR, 95% CI: 1.53, 1.13 – 2.06; P = 0.0046). In both univariate and multivariate analyses, gestational age at booking third trimester and previous ante-natal clinic visits during the index pregnancy were significantly associated with asymptomatic malaria in pregnancy. Low



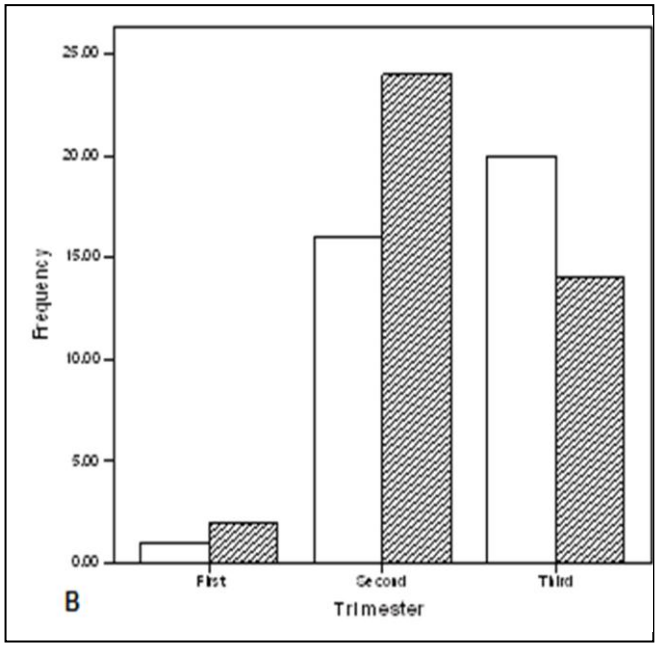




**Figure 2.**
Distribution of asymptomatic (unshaded bars) and symptomatic (shaded bars) malaria in respect to gravidity (A and gestation age (B)

asexual parasitaemia (< 2000 asexual parasite/µL of blood) was an independent predictor of asymptomatic malaria. (Table 2).

## DISCUSSION

Malaria infection in pregnancy in areas of stable malaria have been described as mostly asymptomatic by a number of investigators including Anorlu and others (Anorlu *et al*., 2001) Falade and others (Falade *et al*., 2008); Nwagha and others (Nwagha *et al*., 2009) but some investigators have suggested otherwise (Bardají *et al*., 2008; Tagbor *et al*., 2008). The incidences of asymptomatic and symptomatic malaria in our study were 48 and 52%, respectively indicating that (marginal) majority of our subjects were symptomatic and similar to 51% reported by Bardaji and others. We opine that the non-specific nature of commonly presented symptoms such weakness, headache and body-aches may be ignored unless such individuals are specifically asked. It is our view that asymptomatic malaria parasitaemia in pregnancy might have been over-represented sequel to the mildness and nonspecific nature of symptoms and perhaps coupled with relative passivity of most care-givers. As was observed by Tagbor *et al*., 2008 and Bardaji *et al*., 2008 most malaria associated symptoms in stable malaria areas are non-specific.

It may therefore be challenging deciding whether the nonspecific symptoms recorded in this study were due to malaria or some other conditions including normal pregnancy associated physiological changes. That the affected individuals responded to malaria treatment may be supportive of the origin of such symptoms. It is noteworthy that very few individuals with malaria presented with fever or history of fever in this study. Fever may be relatively more suggestive of malaria and other infective processes than other symptoms that were relatively more commonly reported in this study. Some other studies have also reported low fever incidence (Falade *et al*., 2008; Tagbor *et al*., 2008). Young gestational age of symptomatic parasitaemic subject may suggest that symptomatic malaria promotes early booking for ante-natal care.

In concordance with Tagbor and others, we did not observe association between gravidity and symptomatic malaria parasitaemia. However, Bardaji and others reported significant proportion of clinical malaria in primigravid. This study suggests that pregnant women in their third trimester and prior ante-natal visit(s) were associated with asymptomatic malaria parasitaemia; the influence of accessibility to health facility and antimalarial medication could not be immediately ascertained. It was also observed that parasitaemia of < 2000 asexual parasites/µL blood was a predictor of asymptomatic malaria.

The significantly higher gametocyte carriage detected in asymptomatic subjects may suggest subclinical malaria could have encouraged gametocyte carriage in these subjects. This finding is in agreement with previous report that non-pyrexia

malaria infection favours gametocyte generation (Price *et al*., 1999). The higher gametocyte carriage rate in asymptomatic pregnant women suggests that they may constitute a reservoir of infection. Larger studies on the gametocyte carriage in pregnant women and potential for transmission of malaria in highly endemic areas should be considered.

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