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ADVERSE OBSTETRIC OUTCOMES AMONG WOMEN WITH PLACENTAL MALARIA FROM PERI-URBAN GHANA.

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ABSTRACT

Placental malaria (PM) poses a major threat to both the mother and the unborn child. Maternal anemia and intrauterine growth retardation are major consequences of PM. The risk of dying from malaria is also higher among pregnant women than the general population as high levels of parasitaemia, hypoglycemia, acute pulmonary edema, foetal distress, premature labour, spontaneous abortions and still births are common among pregnant women with malaria.

This case control study examined maternal outcomes in 420 pregnant women (220 with PM as case and 200 without PM as control) attending antenatal clinics at Pramso, a high malaria transmission area in Ghana. PM was high (12.3%) in the study area despite the implementation of the recommended World Health Organization (WHO) guidelines for interventions. Maternal anemia was significantly higher ($p<0.001$) in pregnant women with PM than those without PM. Parity ($p<0.001$), Premature rupture of membranes (PROM) ($p< 0.001$), foul smelling liquor (FSL) $p< 0.05$) and Meconium stained amniotic fluid (MSAF ($p<0.001$) were found to be associated with placental malaria. Primiparous pregnant women were more likely to have PM than multiparous pregnant women. The frequencies of PROM, FSL, MSAF were significantly higher in pregnant women with PM than those without. Ante and Post partum Haemorrhage (APH/PPH) and Pregnancy-induced hypertension (PIH) on the other hand had no statistically significant association with PM. Antenatal care should intensify the implementation of the WHO guidelines as well as prevention and prompt management of the adverse obstetric outcomes associated with PM.

Keywords: placental malaria, maternal outcome, premature rapture of membrane, meconium stained amnoitic fluid,

INTRODUCTION

Placental malaria is caused by *Plasmodium falciparum*-infected erythrocytes that bind the placenta. The binding is mediated by VAR2CSA - a parasite antigen coded by the var gene - which interacts with chondroitin sulfate A (Tuikue-Ndam et al., 2015) Placental malaria poses a major threat to both the mother and the unborn child (Singh et al., 2014; De Beaudrap et al., 2013; Bardaji, et al., 2011; Faladel et al., 2010). Maternal anemia and intrauterine growth retardation have been widely reported in pregnant women with both symptomatic and asymptomatic malaria (Dorman et al., 2002;

Silver et al 2010; Umbers et al., 2011; McGready et al., 2012; De Beaudrap et al., 2013; Singh, 2014) and could account for as high as 23% of maternal death in endemic regions (Faladel et al., 2010). The risk of dying from malaria is also higher among pregnant women than the general population as high levels of parasitaemia, hypoglycemia, acute pulmonary edema, foetal distress, premature labour, spontaneous abortions and still births are common among pregnant women with malaria (Ticconi et al., 2003; Faladel et al., 2008; Saba et al., 2008; De Beaudrap et al., 2013; Singh, 2014). Malaria in pregnancy is also associated with an increased incidence of infant malaria (Le Hesran et al., 1997; Mutabingwa et al., 2005; Schwarz et al., 2008; Bardaji et al., 2011; Le Port et al., 2011).

The WHO has recommended a three prong approach to the prevention and control of malaria during pregnancy in areas of stable transmission through the use of intermittent preventive treatment (IPT) of asymptomatic pregnant women, use of insecticide treated nets (ITNs) and prompt and effective management of acute malaria in pregnancy (WHO, 2004).

Despite the fact that ITNs were freely distributed and there was high coverage of sulfadoxine pyramethamine (sp)-IPT, the prevalence of PM was found to be high in Ghana (Asante et al., 2013), Tanzania (Mosha et al., 2014) and Nigeria (Ibanga et al., 2015).

These adverse consequences of PM, maternal anaemia and intra-uterine growth retardation were mainly attributed to sequestration of parasitized erythrocytes present in the placental intervillous spaces, to chondroitin sulfate A (CSA) in the placenta (Andrews & Lanzer, 2002; Ekweozo, 2010)

Other studies of the pathogenesis of placental malaria implicated immunological protection, transport and metabolism of nutrients, regulation of vasculogenesis and angiogenesis, insulin-like growth factor signaling Axis: regulation of trans-placental transfer of nutrients, cell survival, and proliferation (Dorman et al., 2002; Silver et al., 2010; Umbers et al., 2011; McGready et al., 2012; Conroy et al., 2013; Gazzinelli et al., 2014; Kidima, 2015).

A critical analysis of the pathogenesis of PM suggests other obstetric characteristics especially those found to be associated with a suppressed immune system, bacterial and viral infections and vertical transmission of infections. The study investigated obstetric outcomes that were implicated in other infections to elucidate maternal outcomes of PM.

PATIENTS AND METHODS

Design: Descriptive case-control prospective study was conducted during the period of July 2007 and March 2012.

Sampling: Four hundred and twenty (420) of the 2706 pregnant women seen in antenatal clinics of the St Michael Hospital Pramso, Ghana during the study period were purposively selected and enrolled in the study after informed consent had been obtained. These comprised two hundred and twenty (220) pregnant women with positive PM (cases) and 200 healthy pregnant women who were negative for PM matched for gestational age. Women with known underlining pathology or chronic diseases that have adverse birth outcomes were excluded.

Personal data: Pre-tested questionnaires with a Cronbach's alpha coefficient of 0.88 were used to obtain information on relevant medical, obstetrical and socio-demographic characteristics; history of symptoms suggestive of malaria as well as history of antimalarial usage in the index pregnancy. Maternal haemoglobin, weight, height and body mass index (BMI) were also assessed and recorded.

Placental Malaria Determination: The fixed placental biopsy samples were embedded in paraffin wax and prepared by (Giemsa haematoxylin) eosin and periodic acid Schiff staining in the histopathology laboratory. An experienced consultant clinical microbiologist examined the slides for the presence of malaria parasites, malaria pigments, placental morphology and signs of infection other than malaria. We defined PM as the presence of parasites and/or pigment in the red blood cells or the presence of pigment in the monocytes in the intervillous space of the placenta as described by Bulmer et al (1993).

Obstetric Outcome: Participants were evaluated for presence of premature rupture of membranes (PROM) and premature labour; pregnancy-induced hypertension PIH), foul smelling liquor (FSL), Meconium stained amniotic fluid

(MSAF), bleeding (ante-partum and post partum) and mode of delivery.

Ethical consideration: The Institutional Review Board of the University of Cape Coast approved the study and ethical clearance was obtained from the hospital. Participants' also signed informed consent and participation was voluntary.

Data analysis: Data was analyzed with SPSS 21. For the univariate analysis of categorical variables, Pearson's Chi square or Fisher's exact test was used. For continuous variables, we used the Independent sample t-test after checking normality and equality of the variance on the basis of Levine's test at 5% significant level.

RESULTS

Table 1: Socio-demographic Characteristics of Respondents

Parameters	Variables	Case (n=220)	Control (n=200)	X^2	p-value
Age	<20	7	8	2.194	0.5331
	20 – 29	132	126		
	30 – 39	72	70		
	≥ 40	9	16		
Income	Low	125	119	0.4011	0.8181
	Medium	68	74		
	High	27	27		
Educational Level	Illiterate	54	64	2.9575	0.3982
	Primary	102	90		
	Secondary	52	48		
	Tertiary	12	18		
Residence	Rural	164	156	0.5615	0.4587
	Urban	56	64		

Table 2: Maternal Obstetric Characteristics of Respondents

Parameters	Variables	Case (n=220)	Control (n=200)	X^2	P-Values
Haemoglobin	<10g/dL	116	68	14.174	0.0002
	≥10g/dL	104	132		
Parity	1	134	82	61.624	0.0000
	2	56	85		
	≥ 3	30	53		
PROM	Present	46	4	33.336	0.0000
	Absent	174	194		
APH/PPH	Present	45	42		0.9863
	Absent	175	158		
PIH	Present	12	8	0.2206	0.6383
	Absent	208	192		
FSL	Present	18	6	4.3036	0.0303
	Absent	202	194		
MSAF	Present	69	40	6.4007	0.0110
	Absent	151	160		

During the study period a total of 220 pregnant women with PM were identified out of the 2706 recruited. The prevalence of placental malaria was found to 12.3% (220/2706). The participants were fairly young with mean age of 24 $\pm$ 4.8 years of case and 23.9 $\pm$4.7 years for the control group. The mean haemoglobin was 9.8 $\pm$ 2.3g/dL and 10.6 $\pm$1.9g/dL for those with PM and those without PM respectively.

Table 1. shows the socio demographic characteristics of the participants. Most of them were rural dwellers, 74.5% of case and 78% of the control group. The majority had at least nine years of formal education, 75.4% for case and 68% for control, whereas 57% of case and 59.5% of control were of the low income group. The socio-demographic characteristics of the two groups were comparable.

Table 2 shows obstetric characteristics of the participants, anaemia was significantly higher ($p<0.001$) in pregnant women with PM than those without PM.
Parity ($p<0.001$), Premature rupture of membranes (PROM) ($p< 0.001$), foul smelling liquor (FSL) $p< 0.05$) and Meconium stained amniotic fluid (MSAF ($p<0.001$) were found to be associated with PM. Primigravidae pregnant women were more likely to have placental malaria than multigravidae pregnant women. The frequencies of PROM, FSL, MSAF were significantly higher in pregnant women with PM than those without PM.
There was no statistically significant difference in Antepartum and Post partum Haemorrhage (APH/PPH) and Pregnancy-induced hypertension (PIH) between pregnant women with placental malaria and those without placental malaria.

DISCUSSION

Placental malaria was prevalent among pregnant women in the study area (12.3%). The association between placental malaria, parity and maternal anaemia would be discussed.
The study identified adverse effects of PM during pregnancy on obstetric outcome in the subjects. Premature rapture of membrane, foul smelling amniotic fluid, meconium stained amniotic fluid would also be discussed.
Several studies (Clerk et al, 2009; Asante et al 2013; Mosha et al 2014; Ibanga et al., 2015; Tuikue Ndam et al., 2015) have found that placental malaria was high though pregnant women were given ITNs free of charge and also participated in IPT. This is consistent with the findings in this study. Though the recorded 12.3% is slightly lower than what were recorded in earlier studies, the present study did not consider ITNs usage and IPT coverage. Agudelo et al (2013) reported a prevalence of 3.3% using microscopy and 16.5% using PCR in their subjects. The efficiency of the methods of PM detection could play a major role in the prevalence rate. The prevalence rate in this study could be under reported.
The findings of this study show parity influenced the susceptibility to PM with primigravidae being more susceptible compared to multigravidae. This is consistent with findings of other studies reported earlier (Ticconi et al., 2003; Faladel et al 2008; De Beaudrap et al 20013; Singh et al 2014). However, similar studies found no such significant association (Bako et al., 2009; Ofori et al., 2009; Ibanga et al, 2015). This was attributed to the fact that same proportions of women across various parity received ITNs and also at least two doses of IPT which was not investigated in the current study.
Maternal anaemia was significantly higher in the subjects with PM than those without. Various studies have also linked placental malaria to maternal anaemia (Saba et al 2008; Silver et al., 2011; Mosha et al., 2013; Tuikue-Ndam et al., 2015). Contrary observations were made by (Van Eijk et al., 2001; Al-Farsi et al., 2011; Ibanga et al., 2015) who attributed their findings to the fact that their participants were booked and received antenatal care (ANC) to manage risk factors of anaemia as well as correction of the anaemia by receiving haematinics. In the present study setting antenatal care requires pregnant women are monitored and managed for anaemia. Haematinics are also provided on each ANC visit. However, the study design did not include the number of ANC visits to assess the utilization of such a facility by the participants. Other risk factors of maternal anaemia such as HIV infection and poor nutrition were also not considered.
The results of this study show a significant positive association between PROM, MSAF, FSL and PM. However, there was no significant association between PM and PPH/PIH. Evidence regarding placental malaria and maternal outcomes such PROM, MSAF and FSL are lacking. Maternal anaemia and PM seem to be the focus of most studies. Previous studies have elucidated the mechanism of membrane rapture in PROM in infections (Simmons et al., 2010; Bhutta et al., 2010; Siakwa et al., 2014). They postulated that macrophages release metalloproteinase that degrade amniotic membranes predisposing them to rapture. The role of macrophages and inflammatory cytokines and chemokines in PM has been well described

(Abrams et al., 2003; Kidima, 2015). It would therefore not be out of place to suggest that the mechanism could be the same. Also, infected erythrocyte sequestration has been documented to be involved in reduction in oxygen supply that could lead to hypoxia and subsequent tissue damage (Dorman et al., 2002; Silver et al 2010). This tissue damage could lead to PROM.

The significantly high level of FSL and MSAF could be a result of intrauterine infection. It has been reported that PM results in significant change in syncytiotrophoblast functions (Kidima, 2015) with consequences of hypoxia, immune impairment, trans-placental circulatory inhibition and increased vertical transmission of infections (Dorman et al., 2002; Silver et al 2010;Umbers et al., 2011; McGready et al., 2012; Conroy et al 2013; Gazzinelli et al., 2014; Kidima, 2015).

Secondary bacteria and viral infections to PM as a result of altered syncytiotrophoblast functions could promote adverse obstetric outcomes; MSAF and FSL.

CONCLUSI ON

From the findings of the study it was concluded that PM and maternal anaemia were still high despite the prevailing interventions. The significantly higher PROM, FSL and MSAF in PM should be of great concern. The findings underscore proper screening of pregnant women during ANC to identify high-risk groups for prompt intervention. ITNs and IPT coverage must be properly evaluated to enable more effective strategies for widespread usage. Prompt identification of acute malaria and treatment cannot be over emphasized.

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