

Placental Malaria and Hypertensive Disorders of Pregnancy: a Case-Control Study in a Teaching Hospital, Ghana

Abstract

Aim: To determine the prevalence of placental malaria among women with HDP in Ghana, and its effect on fetal and pregnancy outcomes.

Study Design: Case-control study

Place and Duration of Study: Obstetrics and Gynaecology unit of Tamale Teaching Hospital, Tamale, Ghana from 1st September, 2019 to 31st January, 2020.

Methods: The study involved one hundred and twenty (120) parturient women (80 cases vs 40 controls). Cases were parturient women with HDP admitted at the labour ward, whereas controls were normotensive parturient women admitted for normal delivery at the labour ward. Maternal blood was taken for peripheral malaria diagnosis. Placental malaria PM was diagnosed by placenta tissue examination. Data were analysed using GraphPad Prism version 8.0, and $p < .05$ was considered significant.

Results: The overall prevalence rate of PM was 38% (15% in control versus 53% in cases). The proportion of the malaria (placental) positive participants were different from those without PM who delivered via spontaneous vaginal delivery (64% vs 0%, $p = .01$) and tested positive for malaria during the pregnancy (19% vs 42%, $p = .046$). Higher age, being self-employed, preterm delivery complication and non-central cord insertion significantly increased the risk of developing HDP.

Conclusion: There is an increased prevalence of PM among women with HDP, with resultant increased adverse outcomes such as stillbirth. The observed influence of

PMI on expectant mothers and their neonates inform the need to intensify the preventive measures against malaria in pregnancy.

Keywords: Placental malaria; Hypertensive disorders; Pregnancy

Introduction

About 2-10% of complicated pregnancies with associated feto-maternal morbidity and mortality has been attributed to Hypertensive Disorders of Pregnancy (HDP) [1]. Aside haemorrhage and dystocia, HDP has been reported to be the 3rd cause of morbidity and 2nd cause of mortality in West Africa [2]. Clinically, the syndrome characterized by the new onset of raised blood pressure of 140/90 mmHg or more, occurring in a woman after 20 weeks of gestation is referred to as HDP [3]. In Ghana, despite the 2-fold increase (i.e. 9% observed in 2007 and 18% observed in 2017) in the maternal mortality due to HDP within a decade [4], the increased risk imposed by cardiovascular disease (hypertension, diabetes etc) [5] has led to HDP emerging as the number one cause of maternal death in our tertiary centres [6, 7].

P. falciparum is known to be responsible for the most fatal form out of the four *Plasmodium species* known to cause malaria infection in sub-Saharan Africa [8]. It is known that, *P. falciparum* is the only specie able to sequestrate in the placenta in the course of naturally occurring infections and increases the risk of HDP [9]. Pathophysiologically, placental sequestration (placental malaria) following infection of red blood cells (RBCs), and HDP, both cause placental ischemia, release of pro-inflammatory cytokines and endothelial dysfunction [10, 11]. The link between the two conditions is supported by the increase in both conditions during the rainy season [12]. In both conditions, low birth weight and foetal death have been reported as well as a negative impact on blood function and its fractions [12] due to the alterations in

placental physiology [13-15]. Syncytiotrophoblast and structural damage induced fibrinoid deposition ultimately lead to thickening of the placental basal lamina due to PM [16]. There is a relationship between the immunopathologic processes and these placental changes. The reported immunologic response and heightened inflammation are also said to be a consequence of PM induced placental damage [17].

In areas of high malaria endemicity, PM infected women may be asymptomatic and or unresponsive to peripheral blood film microscopy test [18]. Remaining undiagnosed, this asymptomatic PM may gradually result in physiological changes in placental function, subsequently culminating in pregnancy-associated syndromes such as HDP.

An earlier study in Southern part of Ghana revealed that *Plasmodium* infections during pregnancy have adverse effect on the internal structure of the placenta that may also influence perinatal outcomes [19]. The Ahenkorah et al. [19] study recruited only 50 participants and did not consider pregnant women with hypertensive disorders.

This study determined the prevalence of placental malaria among women with HDP in Northern Ghana, and its effect on fetal and pregnancy outcomes.

Methods

Study site

This study was carried out in the Obstetrics and Gynaecology department (maternity ward) of the Tamale Teaching Hospital, a referral centre in Tamale in the Northern Region of Ghana. Tamale, which is the capital of the northern region of Ghana is located geographically between latitude 9°16 and 9° 34 North and longitudes 0° 36 and 0° 57 West. It is an urban area with a total population of about 537,986 according

to the 2012 demographic review document [20]. A 13.4% malaria prevalence rate among pregnant women was recorded in this region [21].

Study design and population

This was a matched case-control study carried out from 1st September, 2019 to 31st January 2020. Pregnant women with hypertensive disorders of pregnancy who were admitted to the labour ward were recruited as cases whereas the controls were normotensive pregnant women admitted to the labour ward for normal delivery.

Inclusion criteria

The diagnosis of the hypertensive disorders of pregnancy was evaluated by a qualified Obstetrician Gynaecologist using the diagnostic criteria of the National High Blood Pressure Education Program Working Group. The presence of any new onset of hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) at ≥ 20 weeks of gestation in the absence of proteinuria or new signs of end-organ dysfunction in a participant was considered gestational hypertension (GH) [22] while the parturient women who had positive urine protein dipstick results were considered as presenting with Preeclampsia (PE) [23]. Also, preeclamptic women who ended up with seizures were diagnosed as having eclampsia. The blood pressure readings were documented on at least two occasions at a four-hour interval. Lastly, gestational hypertension, preeclampsia and eclampsia were collectively termed as hypertensive disorders of pregnancy for the purposes of this study. All participants in this study were singleton pregnant women.

Exclusion criteria

Women with known renal diseases, diabetes, multiple pregnancies, hepatitis, HIV, hypertension prior to pregnancy, cardiovascular diseases, other infections and

haematological conditions were generally excluded to prevent their possible confounding effect on the adverse obstetric consequences related to HDP (for both cases and controls).

Ethical clearance

This study was approved by the Committee on Human Research, Publications and Ethics (CHRPE) of the School of Medicine and Dentistry, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana (CHRPE/AP/330/19). The participation of all the respondents was voluntary after written informed consent was obtained from each of them prior to delivery.

Questionnaire

A semi-structured questionnaire was administered to the study participants to gather information on sociodemographic data including age, occupation and educational status. Obstetric data including gestational age, gravidity, parity, number of antenatal care (ANC) visits, folic acid intake, number of times IPT was taken and foetal outcome data such as stillbirth, mode of delivery, Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score, baby weight (BW), placenta weight and cord length were also gathered. Also included in the information gathered from the questionnaire were; medical history and lifestyle such as smoking status, alcohol intake and exercise. The reliability of the disclosed information on socio-demographic and reproductive history gathered from the mother was evaluated through record reviews of hospital database (patient's folder).

Peripheral malaria

About 2mls of maternal venous samples were taken prior to delivery. Thick and thin smears were prepared from the maternal peripheral blood and stained with 10%

Giemsa stain. Parasites per 200 white blood cells were counted and checked blindly by two expert microscopists.

Placental malaria

After birth, biopsies of the placenta were taken, washed in physiological saline to remove any clotted blood and fixed in 10% neutral buffered formalin. Tissue processing was done using the Leica TP1020 (Leica Biosystems, Germany) tissue processor. Briefly, 3 cm³ sections of the placental tissues were dehydrated (in increasing concentration of alcohol), cleared in xylenes and infiltrated and embedded with paraffin wax. About 3-4µm sections were made using Leica RM2235 microtome. Two slides were prepared, one of which was stained with 10% Giemsa and the other with haematoxylin and eosin (using the Leica ST5010 Autostainer). Mounting was done with DPX (DPX 44581, Sigma) and microscopic examination was done by two expert microscopists.

An established criterion by Bulmer and colleagues, for classifying placental malaria was used: uninfected (no parasites or pigment), acute (parasites in intervillous spaces), chronic (parasites in maternal erythrocytes and pigment in fibrin or cells within fibrin and/or chorionic villous syncytiotrophoblast or stroma), past (no parasites and pigment confined to fibrin or cells within fibrin) [24].

Also, the placenta (cotyledon) was excised with scissors, allowing maternal intervillous blood to accumulate at the site and a 5-mL sample of heparinized maternal intervillous blood collected together with placental smear using the pool-biopsy methods for parasitological studies [25]. Parasites per 200 white blood cells were counted microscopically. The sampling protocols have been summarized in Figure 1.

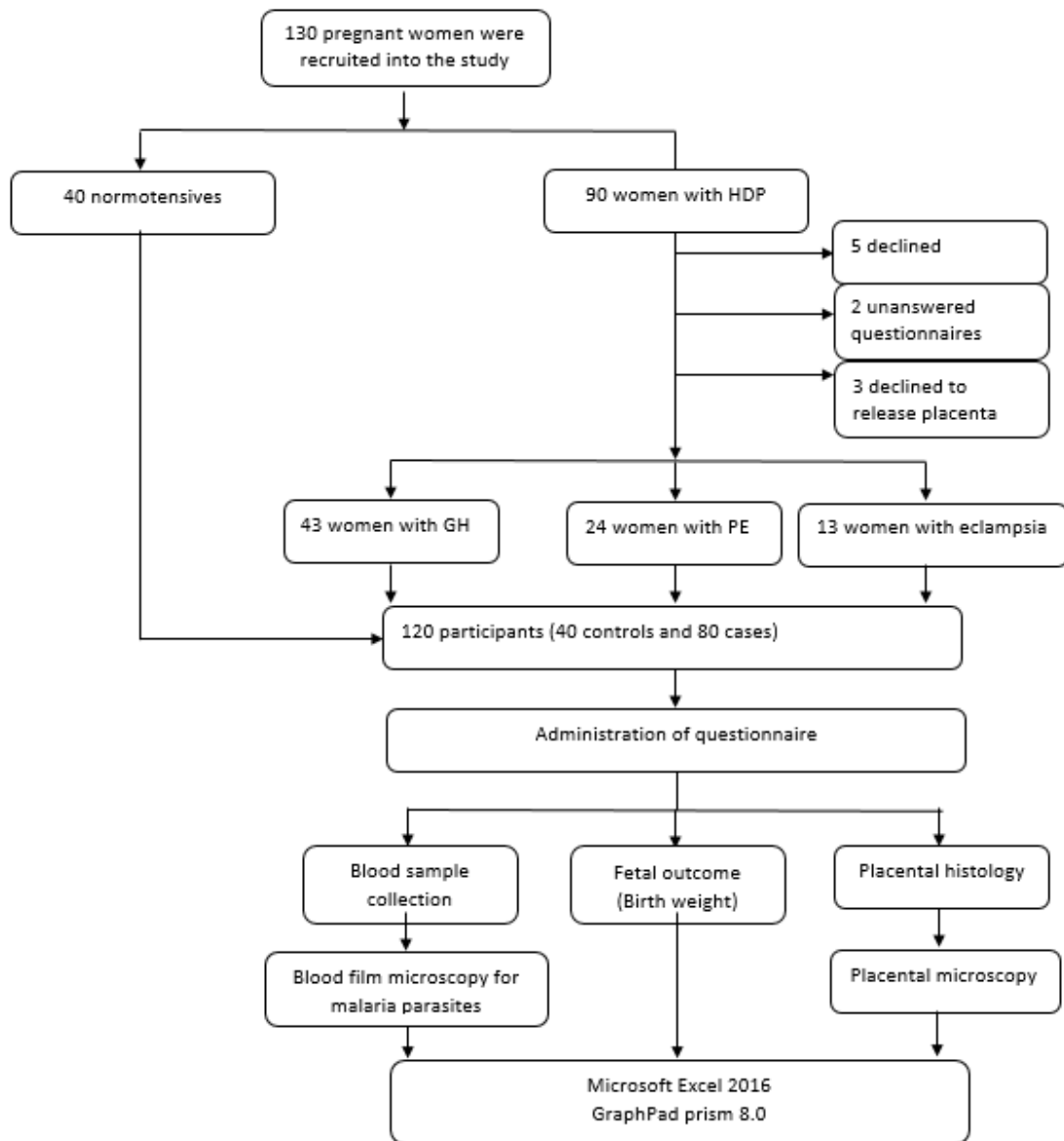


Figure 1: Flow chart of the sampling protocols

Statistical analysis

Data was analysed using Microsoft Excel 2016 and GraphPad Prism version 8.0 (California, USA). Continuous data were presented as means and standard deviations, and were compared using the unpaired Student T-Test, whereas categorical variables were presented as frequencies and percentages and were compared using the Chi-squared test. One-Way ANOVA was used to compare the significant differences between more than two variables. Bivariate and adjusted logistic regression were used

to determine the clinical and obstetric determinants of HDP. A $p < .05$ was considered significant.

Results

Response rate

This hospital-based cross-sectional case control study, was set out to be conducted among 90 pregnant women with hypertensive disorder of pregnancy (HDP) and 40 normotensive pregnant women as control. All the 40 controls accepted, filled the questionnaire and the placenta sample was taken after the informed consent. Out of the 90 pregnant women with HDP contacted for the study, 5 refused to partake in the study, 2 participants returned incomplete questionnaires and 3 refused blood and placenta samples to be taken after filling the questionnaire. The response rate was thus 88.9%.

A total of one hundred and twenty participants (80 cases and 40 controls) were included in the study.

General Characteristics of the Study Population

The ages of the women ranged from 18 to 49 years with a mean \pm SD of 28.7 ± 6.37 years. Nulliparity constituted about 35% of the study population (42 out of 120) while primigravida constituted about 25% of the population (30 out of 120). From the total study population, the mean \pm SD of the parity, gravidity and gestational age are 1.53 ± 1.50 , 2.84 ± 1.57 and 38.13 ± 2.57 , respectively. The foetal outcome indicates the mean \pm SD of 2.74 ± 0.65 kg, 21.39 ± 3.25 cm, 0.55 ± 0.20 kg, 52.68 ± 6.67 cm and 1.86 ± 0.26 cm for baby weight, placenta weight, placenta width, cord length and cord diameter (Table 1).

About 7% of the study population had treated malaria during the pregnancy with a mean \pm SD usage of IPT and number of antenatal visits of 2.06 ± 1.31 and 6.08 ± 2.47 , respectively. Approximately 92% of the participants were on folic acid and 14.2% had known family history of hypertension. About 30% of the participants delivered via caesarean section (CS), 6.7% had stillbirth, 25.8% were admitted at Neonatal Intensive Care Unit (NICU) and 16.7% had preterm delivery as shown in Table 1.

When the study population was stratified based on case and control, there was no significant difference between the mean age of case and control. The average parity, gravidity, number of IPT taken were significantly higher ($p=.033$, $.004$ and $.01$, respectively) when the cases (1.74 ± 1.59 , 3.13 ± 1.60 and 2.53 ± 1.28 , respectively) were compared to the controls (1.13 ± 1.18 , 2.25 ± 1.37 and 1.83 ± 1.26 , respectively) (Table 1). However, the cases had a significantly lower ($p= .02$, $<.001$, $.01$, and $.001$, respectively) mean gestational age, baby weight, placenta width and placenta weight as compared to the controls. The proportions of the cases that delivered through CS, had stillbirth, got admitted to NICU and did not carry the pregnancy to term were significantly higher among the cases compared with the controls (46.25% vs 0%, $p<.001$; 10% vs 0%, $p<.001$; 37.5% vs 2.50%, $p<.001$ and 22.50% vs 5%, $p=.02$ respectively) (Table 1).

Table 1: General and Obstetric Characteristics of Population Stratified into Cases and Controls

VARIABLE	TOTAL	CONTROLS	CASES	P-
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	n= (120)	n= (40)	n= (80)	VALUE
Age (yrs.)	28.74±6.37	27.20±5.88	29.51±6.49	.06
Parity	1.53±1.50	1.13±1.18	1.74±1.59	.03*
Gravidity	2.84±1.57	2.25±1.37	3.13±1.60	.004*
Gestational Age (weeks)	38.13±2.57	38.88±1.45	37.75±2.91	.02*
BMI	27.76±6.58	26.61±4.63	28.34±7.32	.18
SBP (mm/Hg)	140.10±26.00	112.50±12.60	154±18.96	< .001*
DBP (mm/Hg)	90.55±17.51	72.00±9.57	99.83±12.47	< .001*
Obstetrics				
Baby Weight (kg)	2.74±0.65	3.11±0.39	2.55±0.67	< .001*
Placenta Width (cm)	21.39±3.25	22.48±3.54	20.85±2.98	.01*
Placenta Weight (kg)	0.55±0.20	0.63±0.22	0.50±0.17	.001*
Fetal Weight/Placenta Weight	5.58±3.73	5.30±1.18	5.71±4.50	.57
Cord Length (cm)	52.68±6.67	53.48±6.50	52.28±6.76	.36
Cord Diameter (cm)	1.86±0.26	1.80±0.20	1.90±0.28	.06
Malaria During Pregnancy				
Yes	8(6.67%)	2(5%)	6(7.5%)	.61
ANC Visits	6.08±2.47	5.85±1.59	6.20±2.81	.47
No. of IPT Taken	2.06±1.31	1.83±1.26	2.53±1.28	.01*
Folic Acid				
Yes	110(91.67%)	38(95%)	72(90%)	.35
Family History of Hypertension				
Yes	17(14.17%)	4(10%)	13(16.25%)	.36
Mode of Delivery				
SVD	83(69.12%)	40(100%)	43(53.75%)	< .001*
CS	37(30.83%)	-	37(46.25%)	
Foetal Outcome				
Normal	81(67.50%)	39(97.50%)	42(52.50%)	< .001*
NICU	31(25.83%)	1(2.50%)	30(37.50%)	
Still Birth	8(6.67%)	-	8(10%)	
Delivery Complication				
Term	100(83.33%)	38(95%)	62(77.50%)	.02*
Preterm	20(16.67%)	2(5%)	18(22.50%)	

Categorical data are presented as proportions and compared using Pearson Chi-square whilst continuous data are presented as Mean ± SD and compared using Student T-Test. * $p < .05$ was considered statistically significant. BMI= Body mass index, SDP= Systolic blood pressure, DBP= Diastolic blood pressure, NICU= Neonatal intensive care unit, SVD= Spontaneous vaginal delivery, CS= Caesarean section, ANC=Antenatal care

Prevalence of Malaria among Cases and Controls

The prevalence of placental malaria was significantly higher among cases and controls (53% vs 15%, $p < .001$). Also, the overall prevalence of placental malaria was higher than that of peripheral malaria (40% vs 2%, $p < .001$) as shown in Figure 2.

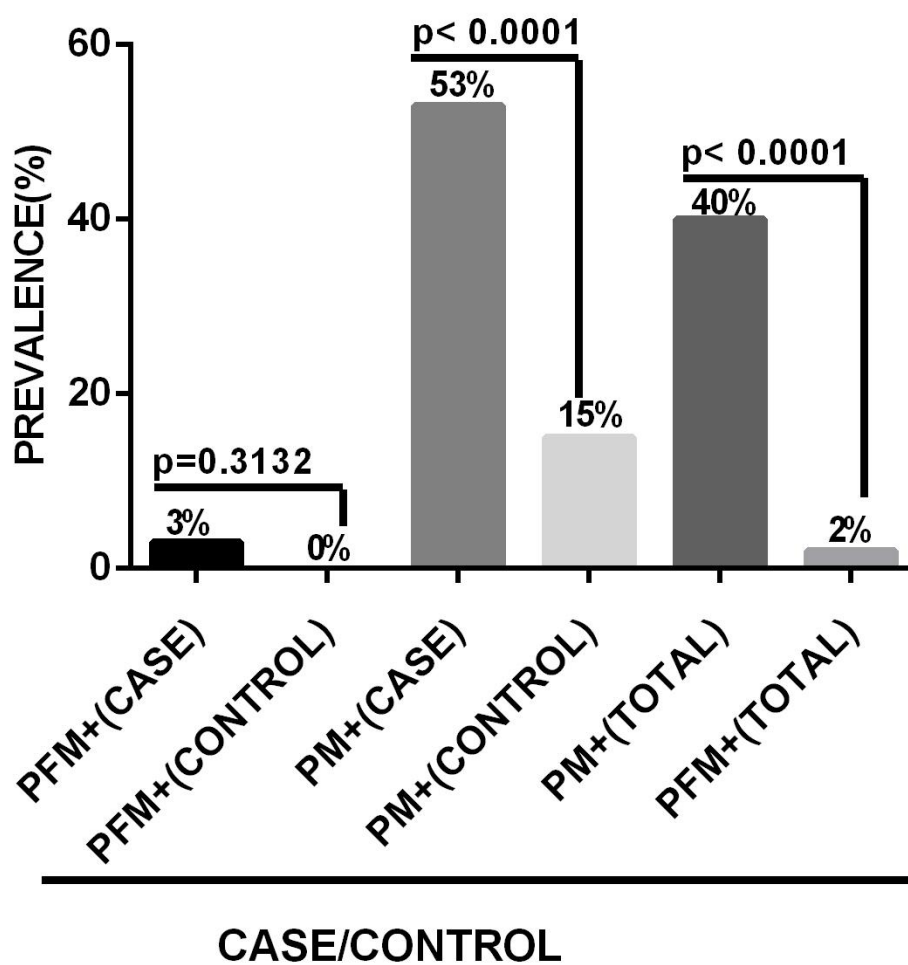


Figure 2: Prevalence of malaria among cases and controls

The data were compared using unpaired Student T-test; PFM = Peripheral Malaria, PM = Placental Malaria

General characteristics of study population stratified into women without PM and HDP (-PM/-HDP), women with only HDP (-PM/+HDP), women with only PM (+PM/-HDP) and women with both PM and HDP (+PM/+HDP).

As shown in Table 2, thirty-four, thirty-eight, six and forty-two were women without PM and HDP (-PM/-HDP), women with only HDP (-PM/+HDP), women with only PM (+PM/-HDP) and women with both PM and HDP (+PM/+HDP), respectively (Table 2).

The mean \pm SD of gravidity among women without PM and HDP (2.38 ± 1.42) was significantly lower ($p=.04$) than that of women with only HDP (3.17 ± 1.51). Also, the proportions of women without PM and HDP who delivered via CS, had their babies admitted at NICU and had preterm delivery were significantly lower compared to women with only HDP (0% vs 58%, $p<.001$, 3% vs 39%, $p<.001$ and 3% vs 21%, 0.02, respectively). However, the average gestational age (38.97 ± 1.24 weeks), APGAR score at 1 minute (7.41 ± 0.93) and 5 minutes (8.68 ± 0.73), baby weight (3.16 ± 0.34 kg), placenta weight (0.64 ± 0.23 kg) and number of times IPT was taken (2.74 ± 1.14) by women without PM and HDP were significantly higher than that of women with HDP only (37.72 ± 3.06 weeks, $p=.03$; 6.69 ± 1.65 , $p=.03$; 7.97 ± 1.40 , $p=.01$; 2.54 ± 0.77 kg, $p<.001$ 0.49 ± 0.21 kg, $p=.01$ and 1.76 ± 1.15 , $p=.001$ respectively).

The proportion of women without PM and HDP who delivered through spontaneous vaginal delivery (100%) were significantly higher ($p<.001$) as compared to women with only HDP (42%). For women with PM only, the mean \pm SD of baby weight (2.82 ± 0.54 kg) and number of times IPT (1.33 ± 1.51) was taken were significantly lower (and 0.01, respectively) as compared to the women without PM and HDP (3.16 ± 0.34 kg, $p=0.046$ and 2.74 ± 1.14 , $p=0.01$ respectively). Again, the proportion of

women with PM only who had malaria during the pregnancy (33%) was significantly higher than that of women without PM and HDP (0%, $p=.001$).

For women with both PM and HDP conditions, the average gestational age (37.94 ± 2.63 weeks), APGAR score at 1minute (5.50 ± 3.07) and 5minutes (6.69 ± 3.43), baby weight (2.60 ± 0.69 kg), placenta width (20.91 ± 3.39 cm), placenta weight (0.53 ± 0.17 kg) and number of times IPT was taken (1.81 ± 1.33) were significantly lower in comparison with women without PM and HDP (38.97 ± 1.24 weeks, $p=.04$; 7.41 ± 0.93 , $p=.001$; 8.68 ± 0.73 , $p=.002$; 3.16 ± 0.34 kg, $p<.001$; 22.74 ± 3.71 cm, $p=.04$; 0.64 ± 0.23 kg, $p=.03$ and 2.74 ± 1.14 , $p=.004$ respectively).

The proportion of the placental positive participants who tested positive for malaria during the pregnancy (19%), delivered via spontaneous vaginal delivery (64%) and had still births (64%) were significantly higher ($p=.01$, $.05$ and $.01$ respectively) as compared to placental negative participants (19% vs 0%, $p=.01$; 64% vs 42%, $p=.047$ and 64% vs 0%, $p=.01$, respectively) as shown in Table 2 .

Table 2: General characteristics of study participants stratified by the presence or absence of PM and HDP.

VARIABLE	-PM/-HDP N= (34)	+PM/-HDP N= (6)	-PM/+HDP N= (38)	+PM/+HDP N= (42)	P VALUE
Age (yrs)	27.76±6.15	24.00±2.37	29.31±5.68	28.53±5.853	.60
Parity	1.18±1.27	0.67±0.52	1.76±1.60	1.719±1.550	.92
Gravidity	2.38±1.42	1.67±0.52	3.17±1.51*	3.031±1.596	.73
Gestational Age (weeks)	38.97±1.24	38.33±2.42	37.72±3.06*	37.94±2.627 ^o	.77
BMI	27.00±4.67	24.37±3.99	28.84±9.32	29.21±6.455	.86

SBP (Mm/Hg)	113.10±12.61	109.00±13.11	150.10±16.52****	157.7±21.19 ^{eeee}	.13
DBP (Mm/Hg)	72.68±9.53	68.17±9.66	98.14±10.03****	102.4±14.14 ^{eeee}	.19
Obstetrics					
APGAR 1min	7.41±0.93	7.67±0.52	6.69±1.65*	5.500±3.069 ^{eee}	.75
APGAR 5mins	8.68±0.73	9.00±0.00	7.97±1.40*	6.688±3.431 ^{ee}	.78
Baby Weight (kg)	3.16±0.34	2.82±0.54 [†]	2.54±0.77****	2.600±0.6947 ^{eeee}	.36
Placenta Width (cm)	22.74±3.71	21.00±1.90	21.14±3.15	20.91±3.392 ^e	.76
Placenta Weight (kg)	0.64±0.23	0.56±0.13	0.49±0.21**	0.5317±0.1659 ^e	.26
Fetal Weight/Placenta Weight (kg)	5.34±1.26	5.11±0.65	4.92±1.05	5.116±1.763	.09
Cord Length (cm)	53.50±6.63	53.33±6.28	51.07±5.69	53.09±7.822	
Cord Diameter (cm)	1.81±0.20	1.78±0.21	1.80±0.24	1.922±0.2744	.17
Malaria During Pregnancy					
Yes	-	2(33%) [‡]	-	8(19%) ^{ee}	.01
ANC Visits	5.79±1.59	6.17±1.72	6.17±2.97	6.063±2.675	.88
No. of IPT Taken	2.74±1.14	1.33±1.51 [†]	1.76±1.15**	1.813±1.330 ^{ee}	.87
Folic Acid					
Yes	33(97%)	5(83%)	37(97%)	35(83%)	.11
Family History of Hypertension					
Yes	3(9%)	1(17%)	9(24%)	4(10%)	.12
Mode of Delivery					
SVD	34(100%)	6(100%)	16(42%)****	27(64%) ^{eee}	.047
CS	-	-	22(58%)****	15(36%) ^{eee}	.047
Foetal Outcome					
Normal	33(97%)	6(100%)	23(61%)***	21(50%) ^{eeee}	.34
NICU	1(3%)	-	19(39%)****	13(31%) ^{ee}	.58
Still Birth	-	-	-	8(19%) ^{ee}	.01
Delivery Complication					
Term	33(97%)	5(83%)	30(79%)*	33(79%) ^e	.91

-PM/-HDP= those without placental malaria and no hypertensive disorder of pregnancy, -PM/+HDP= only hypertensive disorder of pregnancy, +PM/-HDP= only placental malaria, +PM/+HDP= both placental malaria and hypertensive disorder of pregnancy. Data were compared using One-Way ANOVA and statistical significance was set at $p < .05$. PM=Placental malaria, HDP= Hypertensive disorders of pregnancy, BMI= Body mass index, SDP= Systolic blood pressure, DBP= Diastolic blood pressure, NICU= Neonatal intensive care unit, SVD= Spontaneous vaginal delivery, CS= Caesarean section, APGAR= Appearance, Pulse, Grimace, Activity and Respiration, ANC= Antenatal care

Logistic regression of the clinical and obstetric risk factors of HDP among the study population.

Higher age (OR=2.46, 95% CI=1.06-5.69; $p=.04$ for ≥ 30 years), being self-employed (OR=3.74, 95% CI=1.33-10.51; $p=.01$), preterm delivery complication (OR=1.71

95% CI=0.19-3.22, $p=.03$) and non-central cord insertion (OR=4.48, 95% CI=1.78-11.32; $p= .001$) significantly increased the risk of developing HDP from the univariate analysis as shown in Table 3.

After adjusting for confounding variables like age, occupation, delivery complication and cord insertion, the risk factors for HDP among the study group were age (≥ 30 years), occupation (unemployed and self-employed), BMI (obese participants are more at risk), preterm delivery complication and cord insertion (non-central cord insertion) (Table 3).

Table 3: Logistic regression of the clinical and obstetric risk factors of HDP among the study population.

Variable	OR (95%CI)	<i>p</i>-value	AOR (95%CI)	<i>p</i>-value
Age(years)				
<30				
≥ 30	2.46 (1.06-5.69)	0.036	6.13(1.61-23.37)	.01
occupation				
Unemployed	2.44 (0.89-6.72)	0.084	9.09(1.33-62.15)	.02
Self employed	3.74 (1.33-10.51)	0.012	9.37(1.15-76.41)	.04
Gainfully employed				
Education				
No Education	2.00(0.68-5.93)	0.211	0.65(0.03-16.19)	.79
Basic	2.86(0.80-10.20)	0.106	0.24(0.01-7.58)	.43
Secondary	0.86(0.30-2.48)	0.776	1.00(0.04-24.44)	.99
Tertiary				
Gravidity				
Primigravida				
Multigravida	2.15(0.92-5.04)	0.077	1.34(0.30-5.99)	.71
Parity				
Nulliparous				
Multiparous	1.39(0.63-3.04)	0.127	1.24(0.31-5.03)	.76
Malaria During Pregnancy				
No				
Yes	1.54(0.30-8.00)	0.607	0.14(0.01-3.11)	.22
ANC Visits				
<5	1.42(0.57-3.58)	0.452	0.78(0.16-3.72)	.75
≥ 5				
IPT				
Yes	1.49(0.49-4.46)	0.481	0.40(0.06-2.58)	.34

No				
Folic acid intake				
Yes	2.11(0.43-10.44)	0.36	0.99(0.07-14.35)	.99
No				
Family History of Hypertension				
Yes	1.75(0.53-5.75)	0.359	2.23(0.38-13.19)	.38
No				
BMI				
Normal				
Overweight	0.90 (0.38-2.15)	0.808	4.24 (0.69-25.89)	.12
Obesity	1.62 (0.58-4.53)	0.362	12.942 (1.59-105.19)	.02
Delivery complication				
Term				
Preterm	1.71 (0.19-3.22)	0.027	17.72(2.03-154.97)	.01
Cord insertion				
Central				
Not central	4.48 (1.78-11.32)	0.001	4.82(1.20-19.47)	.03
Placental malaria				
Yes	1.30 (0.21-6.8)	0.519	1.10(0.20-5.89)	.41
No				

Logistic regression model was used to determine the Odds ratios and the adjusted odds ratios; OR= Odds ratio, AOR= Adjusted Odds ratio, CI= Confidence Interval, ANC= Antenatal care, BMI= Body mass index IPT= Intermittent Preventive Treatment

Discussion

This study assessed the frequency of occurrence of placental malaria (PM) among women with hypertensive disorders of pregnancy, and to look at the impact of the infection on the fetomaternal outcome. The deposition of infected red blood cells in the intervillous spaces of the placenta (placental malaria) is said to be a characteristic of pregnancy related malaria while peripheral malaria will normally indicate malaria during pregnancy. We found a 1% peripheral malaria rate (0% in control versus 3% in cases) and about 38% placental malaria (PM) rate (15% in control versus 53% in

cases). In this study, malaria parasitaemia was higher in the placenta compared to the peripheral blood of the pregnant women and this is similar to earlier studies. The above finding may be related to the enhanced sequestration of the malaria parasites by the placenta and, this would eventually lower the peripheral parasite density and could affect microscopic detection in blood samples [26, 27].

The prevalence of PM observed in this study is higher than reports from earlier studies elsewhere: 8% reported in Tanzania [28], 11% in the Ashanti region [29] and the Greater Accra region of Ghana [19], and in Tanzania [30]. It is however similar to that observed by Ofori *et al* in 2009 (36%) in the Greater Accra region of Ghana [31]. Our finding is nonetheless lower than the 48% observed in a recent study by Obiri *et al.*, also in the Greater Accra region of Ghana [32] and the prevalence as reported by Fehintola and his colleagues in 2016 in their Nigerian study [33].

The observed differences could be due in part to the different settings and its associated disparities in malaria endemicity, the differences in immunity of the study participants, IPT usage, diagnostic methods as well as time differences [34]. For instance, this study was conducted in the northern part of Ghana which is a notable malaria endemic area as compared to the southern part. Additionally, patronization and use of IPT and ITN has been shown to be lower among the northern parts of Ghana compared to the south [35, 36].

This study showed a higher rate of PM among women with HDP as compared to those without HDP, and this is consistent with previous studies [37-40]. However, it is worth noting that other studies found contrasting results [13, 41]. The pathophysiology of PM-induced hypertension has been linked with placental ischemia

and loss of the integrity of the placenta which results in an increased production of pro-inflammatory cytokines and hence endothelial dysfunction [42, 43].

Sub-Saharan Africa accounts for about 90% of the world malaria infection with 40% of women being infected with malaria during pregnancy [44]. The effect of the malaria burden during pregnancy does not only affect the mother but poses a significant risk to the fetus and/or neonate [45, 46]. The effects of placental malaria on reduced birth weight have been comprehensively studied [47-50]. Consistent with previous reports, we found a significant association between placental malaria and reduced birth weight. A study in Nigeria [33] and other studies in Africa [41-46] have also reported similar findings.

We also found low uptake of IPT among women who developed PM as consistent with other studies done in sub-Saharan Africa [33, 51]. Specifically, on average, women with PM took the IPT once during the gestational period. This level of uptake is below the WHO recommendation [52] of at least three doses of IPT during the entire pregnancy period, and thus may have potentiated the risk of PM in this group.

The deposition of parasites in the placenta leads to the infiltration of the intervillous space of the placenta by maternal monocytes and secretion of chemotactic β -chemokines which begin the inflammatory cascade by drawing more inflammatory factors and monocytes [53].

Spontaneous vaginal delivery continues to be the commonest mode of delivery worldwide; however, the rate of caesarean section among women with PM was increased in this study. Caesarean sections are used as interventions for women with

adverse pregnancy outcomes to stabilize both the mother and the baby [54], and this intervention has helped to substantially decrease the rate of stillbirths [55].

In this study, increased maternal age showed to be a risk factor for HDP; with women aged ≥ 30 years (AOR 6.13, 95% CI 1.61-23.37) having greater risk of developing HDP than those who were < 30 years. This finding is consistent with observations from Tanzania (OR 1.10, 95% CI 1.03–1.20) [56] as well as other countries [57, 58]. Other studies in Ghana and Ethiopia again reported that older age (> 35 years) was a risk factor for hypertensive disorders of pregnancy [59, 60]. Although risk of HDP increases with maternal age, young age has also been recognized to be a risk factor for developing HDP (OR 2.6, 95% CI 1.5–4.7) among Cameroonian women [61]. However, no link was found between blood pressure and maternal age in a study conducted in the southern part of Ghana [62]. The reason for this difference could be due to the variations in the sampling methods, as the [63] study recruited only pregnant women > 20 weeks of gestation.

Our study revealed a 12.94 increased risk of HDP in pregnant women with obesity. Several studies have indicated obesity to be a risk factor for HDP [64-66]. Again, mothers in Tigray region of Ethiopia who were overweight were also at risk of developing HDP as compared to their normal and underweight counterparts (AOR = 5.5 95% CI: 1.12-27.6) [67]. This study further revealed that women who gave birth before 36 weeks of gestation (preterm delivery) had 17.72 higher odds of developing hypertensive states of pregnancy in comparison with their counterparts. These findings were similar to studies in Kumasi, Ghana [68] and Nigeria [69]. This may be due to the fact that delivery of fetus is the only remedy for hypertensive disorders of pregnancy to date.

Also, the risk of developing hypertensive disorders of pregnancy was 4.82 higher among women whose placenta's cord insertion was not centrally placed compared with those whose cord insertion was centrally placed. However, non-central cord insertion was not associated with HDP in a study conducted in 2016 [70]. Placenta with non-central cord insertion exhibits a sparse chorionic vascular arrangement and a significant decrease in transport of nutrient, and this has been associated with small fetus and placenta [71]. Non-central cord insertion has been linked with HDP in other studies elsewhere [72, 73].

Participants for the study were selected from only one site in the northern part of Ghana, and this was noted to be a limitation to the study.

Conclusion

There is an increased prevalence of PM among women with HDP, with resultant increased adverse outcomes such as stillbirth. The observed influence of PMI on expectant mothers and their neonates inform the need to intensify the preventive measures against malaria in pregnancy. **Future study to extensively ascertain the national determinants of PM is recommended.**

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Competing interests

The authors have no conflict of interest.

Consent for publication

Not applicable

Authors' contributions

O.A.M. and S.D. developed the concept and designed the experiments. **O.A.M., S.D. and N.A.** supervised the experimental procedures. **S.D.** collected the sample and conducted the laboratory experiments and acquired the data. **O.A.M., S.D., R.D.T** and **N.A.** analyzed and interpreted the data as well as developed the manuscript. **M.E.A.A., KM, SKA, GA, E.W.O., C.A.G., C.G., W.K.B.A.O., C.N., G.A., E.T., L.D.A, Y.A.W** and **A.Y.D.** provided critical review and edited the manuscript and **O.A.M., S.D., A.Y.D., W.K.B.A.O., C.N., E.T., L.D.A., R.D.T, G.A., Y.A.W, KM, SKA, GA,** and **N.A.** approved the final version for publication.

Consent

The participation of all the respondents was voluntary after written informed consent was obtained from each of them prior to delivery.

Ethics approval and consent to participate

All methods were carried out in accordance with the Helsinki declaration. The study was approved by the Committee on Human Research, Publications and Ethics (CHRPE) of the School of Medicine and Dentistry, Kwame Nkrumah University of Science and Technology (CHRPE/AP/330/19).

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