Original Article

Effects of Malaria Parasitaemia on Foetal Middle Cerebral Artery Doppler Indices in a Cohort of Pregnant Nigerian Women

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ABSTRACT

Objectives: Malaria in pregnancy (MiP) increases maternal and perinatal complications including maternal anaemia and foetal growth restriction (FGR). Middle cerebral artery (MCA) indices obtained using Doppler ultrasound are an important tool in predicting the onset of FGR and perinatal mortality in MiP since ultrasound is cheap, readily available, noninvasive and radiation free. We aimed at comparing foetal MCA Doppler indices in pregnant women with and without malaria. The effect of parasitaemia level on these indices was also evaluated.
Methods: Fifty-eight foetuses of women with MiP and 100 foetuses of age and gestational age matched apparently healthy controls between 24 and 40 weeks were consecutively recruited from the antenatal clinic of our hospital between January and December 2018. Venous blood was taken for peripheral blood film to diagnose and quantify malaria parasitaemia. Foetal MCA Doppler indices of both MiP subjects and controls were determined using real time 2.5–5.5 MHz diagnostic ultrasound machine with Doppler facility.
Results: Mean foetal MCA resistive index, pulsatility index, peak systolic velocity (PSV), end-diastolic velocity, and systolic-diastolic ratio for MiP subjects were 0.81 ± 0.05, 1.65 ± 0.24, 48.31 ± 14.16, 9.72 ± 4.18 and 5.53 ± 1.34 while those for controls were 0.84 ± 0.04, 1.88 ± 0.19, 51.43 ± 11.41, 8.24 ± 2.51 and 6.51 ± 1.02, respectively. Apart from PSV ($P = 0.132$), other indices evaluated showed statistically significant difference between the two groups ($P > 0.01$). None of the parameters showed significance association with the level of parasitaemia.
Conclusion: MiP causes detectable changes in the foetal MCA Doppler indices which may indicate foetal distress and also suggest FGR.

Key words: Doppler ultrasound, foetal growth restriction, malaria, middle cerebral artery velocimetry, pregnancy

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INTRODUCTION

Malaria is an infectious disease endemic in many warm regions of the world, caused by obligate intracellular protozoa of the genus *Plasmodium*, usually transmitted to humans by the bite of the female *Anopheles Mosquitoes*.[1] There are five species of these protozoa that cause disease in humans, but two of these species – *Plasmodium falciparum* and *Plasmodium vivax* pose the greatest threat.

P. falciparum is the most prevalent malaria parasite on the African continent and is responsible for most malaria-related deaths globally. *P. vivax* is the dominant malaria in most countries outside of sub-Sahara Africa.

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Malaria transforms normal pregnancy to a pathological one, contributing to at least 10,000 maternal deaths and 200,000 new-born deaths annually.[2] Malaria-associated pregnancy complications include anaemia, spontaneous abortion, prematurity, low birth weight and stillbirth.[3]

The populations at risk include infants, children under 5 years of age, pregnant women and patients with decreased immunity such as human immunodeficiency virus/Acquired immunodeficiency syndrome, as well as non-immune migrants and mobile populations such as travellers.[4] Globally, according to WHO world malaria report 2018, an estimated 3.4 billion people in 92 countries are at risk of being infected with malaria and developing the disease.[5] Each year, more than 125 million pregnant women are at risk of malaria infection, which can

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have serious consequences for them and their offsprings, especially in first and second-time mothers.[6] Not <27.8% of pregnant women are reported to have evidence of placental infection at delivery.[4] In South-West Nigeria, the prevalence of malaria in pregnancy (MiP) ranges from 7.7%[7] to 13%.[4]

Pregnant women, particularly primigravida are more vulnerable to malaria infection because pregnancy causes a reduction in acquired antimalarial immunity (cellular and humoral).[8]

The placenta acts as a filter by retaining the parasitised red cells leading to the deterioration of the placenta and ultimately resulting in a decrease in foeto-placental exchange and reduced foetal nutrition.[2] The middle cerebral artery (MCA) and other cerebral arteries are capable of undergoing auto-regulation to preserve cerebral metabolism and function in the presence of hypoxia. This auto-regulation permits vasoconstriction or vasodilatation to maintain constant perfusion of the cerebral tissues and is controlled by metabolic, neural, and chemical mediators.[9] The blood flow redistribution between the brain and the placenta can be detected and the cerebral responses to hypoxia determined using Doppler ultrasound.

The MCA is the most studied foetal brain artery because it is more easily accessible.[10] And has been assessed as a predictor of perinatal outcomes.[11]

Using colour flow imaging, the MCA could be seen as a major lateral branch of the circle of Willis running antero-laterally towards the lateral edge of the orbit.[12] Normally, the foetal cerebral circulation is a continuous, forward, low flow with high impedance. In the presence of foetal hypoxemia secondary to placental insufficiency, the blood flow is redistributed to the brain, heart, and adrenal glands, with decreased resistance allowing for increased blood flow and oxygen delivery to the brain.[10] This foetal ability to preferentially supply the cerebral, coronary, adrenal and splenic circulation has been ascribed to the 'foetal head sparing theory' and has been proposed as an early indicator of auto-regulation in cases of intrauterine growth restriction (IUGR).[10]

This study was embarked upon to evaluate changes in the MCA Doppler indices in acute malaria, as well as provide local reference data which is currently lacking in our environment. It also set out to determine foetuses that are at risk of cardiovascular distress from anaemia or hypoxia as these are pointers to foetal IUGR.

METHODS

This cross-sectional case-controlled study was conducted on the foetal MCAs of pregnant women with clinical and laboratory evidence of MiP. The study was performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki, as revised in 2013 and our Institutional Health Research Committee approved the conduct of this research.

A total of 58 pregnant women with clinical and laboratory diagnosis of MiP and 100 age and gestational age (GA)-matched healthy pregnant controls were consecutively recruited from Obstetrics and Gynaecology Department of the hospital. Written informed consent was obtained from each of the participants. The subjects were <45 years of age and were in 24 weeks-GA and above because the MCA is better visualised at this age. Subjects with medical conditions such as urinary tract infection, diabetes and hypertensive conditions in pregnancy were excluded. Multiple gestations and foetuses with congenital anomalies were also excluded.

Study parameters

The subjects' biodata including age, last menstrual period, sex, educational level and hospital number were obtained. Relevant history taking and physical examination for information regarding the exclusion criteria were inquired from the patients. Their hospital records were consulted where necessary.

Venepuncture of the antecubital veins of the left arm was done under sterile conditions for all participants. About 2mls of blood was obtained for blood film for diagnosis and quantification of malaria parasitaemia (using Giemsa staining and examination under light microscope).

Sonographic technique for middle cerebral artery Doppler

With subjects in the supine or semi-recumbent position (as comfortable for the patient), B mode and Doppler ultrasound scanning of the foetal MCA was done with an ultrasound machine (Versana Essential GE Medical Systems, China Co., Ltd) equipped with 2.5–5.5 MHz curvilinear probe. After the acoustic gel has been applied to the skin surface (to reduce acoustic impedance between the skin and transducer surface) and routine obstetric ultrasonography (to obtain foetal biometrics and exclude multiple gestation and foetal anomalies) has been done, the probe was manipulated with the aid of a colour box at the level of the bi-parietal plane until the circle of Willis was displayed [Figure 1]. The measurement was then made at about 2 cm from the origin of MCA and cursor placed at the point of interest using Doppler angle 0–30 using a very small sample volume[12] [Figure 1]. Doppler indices were obtained through automatic tracings. The process was repeated three times and the average of the readings was recorded to minimise intra-observer variation.

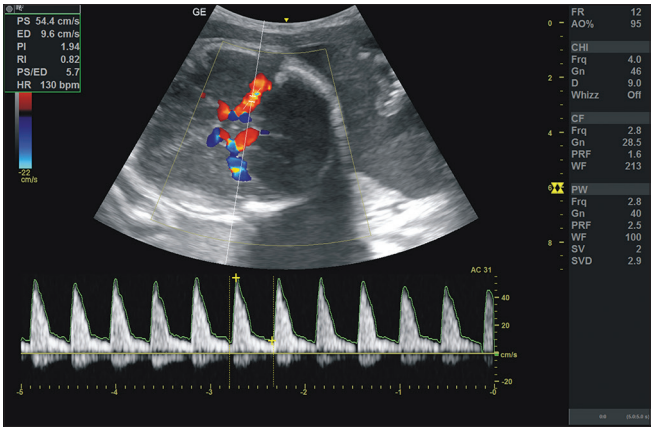

Figure 1: Triplex ultrasound showing Doppler indices of the middle cerebral artery

Data analysis

All data were entered into the computer spreadsheet using the Statistical Package for Scientific Solutions (SPSS) version 20 for Windows (manufactured by IBM Corporation, 2011). Quantitative variables were indicated as mean ± standard deviation and the qualitative variables were indicated as frequencies and percentages. Analysis of variance with Scheffe *post-hoc* analysis was used to compare difference in MCA Doppler indices across various GA. Independent sample *t*-test was used to compare Doppler indices between MiP subjects and apparently healthy controls. The MCA Doppler indices were further compared among MiP subjects with low level of parasitaemia and those with moderate/high level of parasitaemia using box plots and independent sample MannWhitney *U*-test. A $P < 0.05$ was considered statistically significant.

RESULTS

The mean age for MiP subjects was 31.1 ± 5.1 years while that of the control group was 30.5 ± 4.9 years [Table I]. No statistically significant difference is noted in the age, parity and menstrual GA among the two groups ($P > 0.05$).

Level of parasitaemia in the experimental group shows that 53 subjects (91.4%) had between 1 and 10 parasites per 100 high power fields (hpf) (+), 3 subjects (5.2%) had between 11 and 100 parasites per100 hpfs (++) and 2 subjects (3.3%) had 1 and 10 parasites per hpf (+++).

All the Doppler indices evaluated varied significantly with GA among subjects with MiP and controls [$P > 0.05$ and Tables II and III]. Among MiP subjects, the maximum resistive index (RI), pulsatility index (PI), and systolic-diastolic (SD) ratio were recorded between 25 and 29 weeks GA with mean values of 0.85 ± 0.02, 1.91 ± 0.17 and 6.42 ± 1.2, respectively [Table II]. Similar pattern is observed among the control subjects with maximum RI, PI, and SD ratio of 0.88 ± 0.07, 2.09 ± 0.19, and 7.31 ± 0.94 respectively [Table III]. The peak systolic velocity (PSV) and end-diastolic velocity (EDV) increase gradually with GA among the MiP and control subjects with peak values recorded at 35–39 weeks GA [Tables II and III].

There was statistically significant decrease in RI ($P < 0.001$), PI ($P < 0.001$) and SD ratio ($P < 0.001$) among the MiP group compared to the control group whereas the EDV is significantly higher in MiP group compared to the control group ($P = 0.006$). Although mean PSV is lower in MiP group, the difference is not statistically significant [$P = 0.132$ and Table IV].

All the Doppler indices evaluated did not differ significantly between the low and moderate/high grades of parasitaemia [$P = 0.002$ and Figure 2].

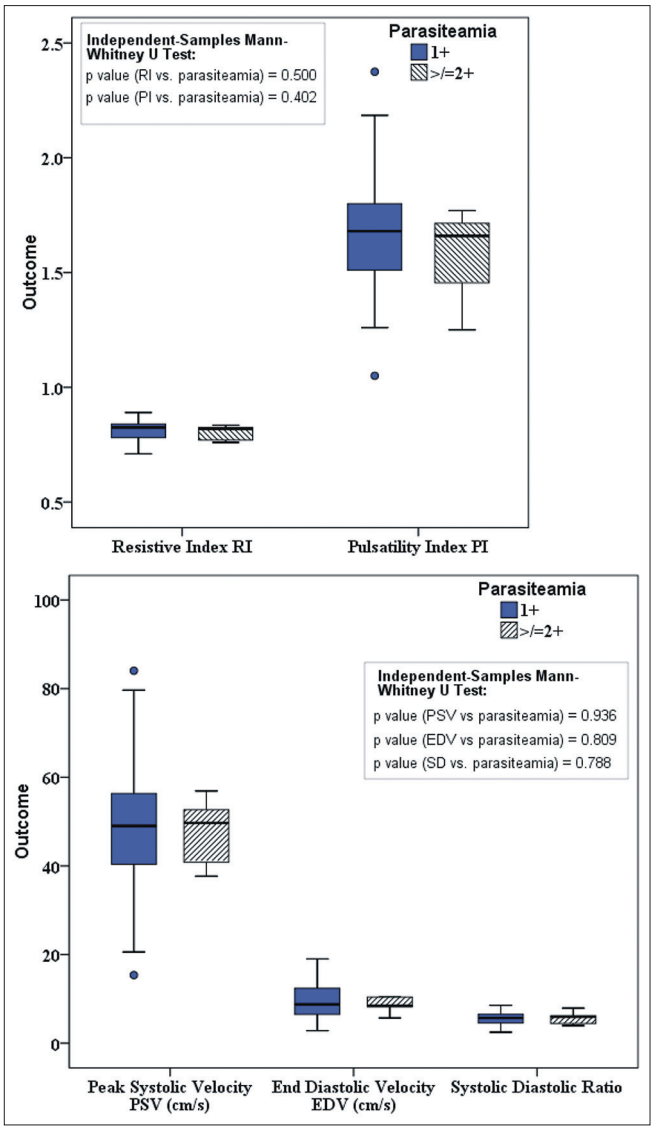

Figure 2: Box plots comparing middle cerebral artery Doppler indices with grades of parasitaemia

DISCUSSION

In this study, majority of MiP subjects (91.67%) had between 1 and 10/100 hpf level of parasitaemia (representing the least severe) while the most severe grades accounted for only 3.33%. This may be a reflection of early detection of cases from antenatal clinics before worsening of symptoms and parasitaemia. Furthermore, Nigeria is endemic for malaria and regarded as an area with moderate-to-intense transmission for the parasite. Partial immunity that is developed over years of exposure reduces the risk of malaria-causing severe disease, especially in adults.

Our study also showed that the Doppler indices varied with changes in GA. The relationship between RI, PI, and SD ratio and foetal GA was parabolic with the highest mean recorded at 25–29 weeks gestation. This is similar to the findings of Mari *et al*.[13] in the USA and Srikumar *et al*.[14] in India. Mari *et al*. evaluated MCA indices in a cross-section of normal foetuses and found that PI values of the MCA were higher at 25–30 weeks' gestation and had parabolic curve. Srikumar *et al*.[14] also evaluated MCA and umbilical artery (UA) Doppler indices in normal pregnancies between 18 and 40 weeks and observed that the MCA RI and PI showed a parabolic curve

Table I: Subjects' demographic characteristics

Variables	Malaria (n=58), n (%)	Control (n=100), n (%)	Statistics	df	P
Age (years), mean±sd* (range)	31.1±5.1 (21-53)	30.5±4.9 (17-41)	0.761*	156	0.448
<25	3 (5.2)	13 (13.0)	0.687#	3	0.875
25-29	22 (37.9)	25 (25.0)			
30-34	17 (29.3)	37 (37.0)			
≥35	16 (27.6)	25 (25.8)			
Parity					
None	15 (25.9)	28 (28.0)	0.272#	3	0.965
One	22 (37.9)	35 (35.0)			
Two	14 (24.1)	23 (23.0)			
>Three	7 (12.1)	14 (14.0)			
Expected EGA					
20-24	6 (10.3)	8 (8.0)	1.562#	3	0.668
25-29	8 (13.8)	18 (18.0)			
30-34	26 (44.8)	37 (37.0)			
35-39	18 (31.0)	37 (37.0)			
Level of parasitaemia					
1-10 per 100 hpf (+)	53 (91.4)	-	-	-	-
10-100 per 100 hpf (++)	3 (5.2)	-			
1-10 per each hpf (+++)	2 (3.4)	-			

*Independent sample t-test, #Pearson Chi-square, significant at P<0.05. hpf: High power field, sd: Standard deviation, EGA: Gestational ages

Table II: Middle cerebral artery Doppler indices in subjects diagnosed of malaria in pregnancy

Middle cerebral artery Doppler indices in subjects with MiP	GA	n=58	Mean±sd	P-values based on Scheffe *post hoc* analysis			
				20-24	25-29	30-34	35-39
RI	20-24	6	0.82±0.04	-	-	-	-
	25-29	8	0.85±0.02	0.716	-	-	-
	30-34	26	0.82±0.04	0.983	0.268	-	-
	35-39	18	0.78±0.05	0.123	0.001	0.025	-
	F, P		6.974, <0.001				
PI	20-24	6	1.65±0.15	-	-	-	-
	25-29	8	1.91±0.17	0.180	-	-	-
	30-34	26	1.63±0.19	0.997	0.020	-	-
	35-39	18	1.57±0.27	0.861	0.005	0.804	-
	F, P		5.034, 0.004				
PSV	20-24	6	39.37±11.97	-	-	-	-
	25-29	8	42.13±6.95	0.985	-	-	-
	30-34	26	47.04±13.74	0.657	0.841	-	-
	35-39	18	55.85±14.95	0.088	0.131	0.212	-
	F, P		3.480, 0.022				
EDV	20-24	6	7.77±2.50	-	-	-	-
	25-29	8	7.44±3.46	0.999	-	-	-
	30-34	26	8.51±3.03	0.975	0.905	-	-
	35-39	18	13.12±4.46	0.024	0.005	0.001	-
	F, P		8.197, <0.001				
SD ratio	20-24	6	4.64±1.27	-	-	-	-
	25-29	8	6.42±1.26	0.061	-	-	-
	30-34	26	5.99±1.19	0.106	0.847	-	-
	35-39	18	4.76±1.11	0.997	0.018	0.014	-
	F, P		6.565, 0.001				

The mean difference is significant at the 0.005 level; F - ANOVA. GA: Menstrual gestational age, MiP: Malaria in pregnancy, sd: Standard deviation, RI: Resistive index, PI: Pulsatility index, PSV: Peak systolic velocity, EDV: End diastolic velocity, ANOVA: Analysis of variance, SD: Systolic diastolic

with a plateau at 28 and 30 weeks of gestation. Their study was also conducted in a tertiary care facility like the index study. The PSV and EDV on the other hand, increased gradually with gestation age and the peaks were recorded at 35–39 weeks. This

Table III: Middle cerebral artery Doppler indices in control subjects

Middle cerebral artery Doppler indices in controls	GA	*n*=58	Mean±sd	*P* value based on Scheffe *post hoc* analysis			
				20-24	25-29	30-34	35-39
RI	20-24	8	0.83±0.02	-	-	-	-
	25-29	18	0.88±0.07	0.083	-	-	-
	30-34	37	0.85±0.02	0.799	0.104	-	-
	35-39	37	0.82±0.03	0.901	<0.001	0.038	-
	F, *P*		8.580; <0.001				
PI	20-24	8	2.01±0.13	-	-	-	-
	25-29	18	2.09±0.19	0.729	-	-	-
	30-34	37	1.86±0.13	0.092	<0.001	-	-
	35-39	37	1.77±0.16	0.002	<0.001	0.106	-
	F, *P*		19.585; <0.001				
PSV	20-24	8	30.87±4.28	-	-	-	-
	25-29	18	42.56±10.10	0.002	-	-	-
	30-34	37	50.29±5.04	<0.001	0.002	-	-
	35-39	37	61.32±6.79	<0.001	<0.001	<0.001	-
	F, *P*		61.071; <0.001				
EDV	20-24	8	4.96±0.72	-	-	-	-
	25-29	18	5.91±1.06	0.445	-	-	-
	30-34	37	7.55±1.19	<0.001	0.001	-	-
	35-39	37	10.79±1.71	<0.001	<0.001	<0.001	-
	F, *P*		78.918; <0.001				
SD ratio	20-24	8	6.29±0.69	-	-	-	-
	25-29	18	7.31±0.94	0.061	-	-	-
	30-34	37	6.78±0.91	0.563	0.214	-	-
	35-39	37	5.90±0.84	0.732	<0.001	0.001	-
	F, *P*		12.384; <0.001				

The mean difference is significant at the 0.005 level, *F* - ANOVA. GA: Menstrual gestational age, sd: Standard deviation, RI: Resistive index, PI: Pulsatility index, PSV: Peak systolic velocity, EDV: End diastolic velocity, ANOVA: Analysis of variance, SD: Systolic diastolic

Table IV: Comparison of foetal middle cerebral artery Doppler indices and some biometric parameters among subjects with malaria in pregnancy and controls

Variables	Malaria (*n*=58)	Control (*n*=100)	Statistics	df	*P*
RI	0.81±0.05	0.84±0.04	−4.879	156	<0.001
PI	1.65±0.24	1.88±0.19	−6.571	156	<0.001
PSV (cm/s)	48.31±14.16	51.43±11.41	−1.515	156	0.132
EDV (cm/s)	9.72±4.18	8.24±2.51	2.775	156	0.006
SD ratio	5.53±1.34	6.51±1.02	−5.182	156	<0.001
Biparietal diameter (cm)	8.04±1.16	7.99±1.05	0.238	156	0.813
Head circumference (cm)	29.54±3.71	29.62±3.47	−0.131	156	0.896
Abdominal circumference (cm)	28.71±5.26	28.49±4.81	0.275	156	0.784
Femur length (cm)	6.29±1.10	6.27±0.97	0.108	156	0.914

RI: Resistive index, PI: Pulsatility index, PSV: Peak systolic velocity, EDV: End diastolic velocity, SD: Systolic diastolic

is in agreement with the finding of Andrei and Vladareanu[15] in their study of rhesus alloimmunised pregnancies where they recorded an increase in MCA-PSV with gestation both in normal pregnancies and rhesus alloimmunised pregnancies. In contrast to our finding however, this increase with GA was only seen up to 34 weeks, above which it declined. The observed difference may be a result of the difference in the clinical entities that were evaluated in the two studies.

We also found statistically significant difference between the MCA Doppler indices across the gestational ages of subjects with and without MiP. All indices except EDV were lower in the subjects with MiP compared to the apparent healthy controls. Our finding is in agreement with many studies on foetoplacental haemodynamic abnormalities.[2,9,16-19] This is in concordance to the findings of Arbeille *et al*.[8] who reported abnormal foetal umbilical and cerebral artery Doppler indices during malaria crisis: UA RI increased by 5%–20% and MCA RI decreased by the same percentage, an indication of flow redistribution to the brain. This finding, like that of our study, can be attributed to acute hypoxia caused by blocking of the placental villi by malaria parasites.

Interestingly, studies have reported associations between abnormal MCA Doppler indices and perinatal outcome. For example, Oros *et al*.[20] and Sharbaf *et al*.[21] have both reported abnormal MCA PI values in small-for-GA foetuses when compared to foetuses that were appropriate for GA showing that MCA Doppler ultrasound is a useful adjuvant for identifying and managing IUGR.

In our study, none of the MCA indices showed a statistically significant difference across the level of parasitaemia. This may be a reflection of the fact that majority of the MiP subjects in the study had low parasitaemia. It is also possible to infer that the presence of malaria parasitaemia and not the quantity is responsible for the observed alterations in the MCA Doppler indices. There is a dearth of publication between malaria parasitaemia grades and cerebral/utero-placental blood flow. Arbeille *et al*.[8] reported no statistically significant association between the parasitaemia grades and the Cerebral-UA resistance ratio similar to our findings. However, a local study by Adelodun *et al*.[22] reported a significant increase in the mean umbilical RI as well as uterine RI and PI across the grades of parasitaemia.

Some of the findings in this study may have been limited by selection bias, as only patients presenting to the hospital were recruited into the study. We however tried to minimize this by consecutively recruiting consenting patients.

CONCLUSION

We conclude from this study that apart from EDV which is higher, all MCA Doppler indices are significantly lower in subjects with MiP compared with apparently healthy control, a sign of blood redistribution to the brain, and we recommend that MCA Doppler should be routinely carried out during obstetric ultrasound scan. This will allow for early detection of any foetal growth faltering that may engender IUGR or foetal demise. Future longitudinal studies evaluating the relationship between parasitaemia grades and cerebral/uteroplacental blood flow in MiP subjects are also recommended.

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Conflicts of interest

There are no conflicts of interest.

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