Original Article

Effect of asymptomatic malaria parasitemia on the uterine and umbilical artery blood flow impedance in third-trimester singleton Southwestern Nigerian pregnant women

Adetayo Mojeed Adelodun, Ademola Joseph Adekanmi[1], Adebola Roberts[2], Abiodun Oludotun Adeyinka[1]

Department of Radiology, University College Hospital, Departments of [1]Radiology and [2]Obstetrics and Gynaecology, College of Medicine, University of Ibadan, Ibadan, Nigeria

ABSTRACT

Background: Asymptomatic malaria parasitemia (AMP) in pregnancy is a major public health issue in tropical countries and represents a vast percentage of malaria infection in pregnancy. It is nonsymptomatic, neglected from treatment but significantly affects uteroplacental and fetoplacental hemodynamic blood flow, with negative pregnancy outcome that includes miscarriages, preterm labor/delivery, low birth weight, and intrauterine fetal death. Doppler ultrasound is a reliable, non-invasive, ionizing radiation-free, and repeatable method in the assessment of uterine and umbilical arteries vascular flow dynamics and resistance in malaria parasitemia in pregnancy.

Materials and Methods: This comparative cross-sectional study was conducted between June 2016 and January 2017 was to assess and compare the vascular flow of the uterine and umbilical arteries in healthy pregnant women with AMP and those without malaria parasitemia in the third trimester of singleton pregnancy using Doppler ultrasound.

Results: The mean uterine arteries Doppler indices were significantly higher in AMP than controls. The mean Doppler indices values for pulsatility index (PI), resistive index (RI), and systolic to diastolic ratio (SDR) were 0.85 ± 0.16, 0.59 ± 0.11, and 2.12 ± 0.17 for the subjects and 0.77 ± 0.09, 0.51 ± 0.06 and 2.05 ± 0.22 for the controls, respectively. These differences were statistically significant: PI was ($P < 0.001$; 95% confidence interval [CI]: −0.11, −0.051), RI was ($P < 0.001$; 95% CI: −0.10, −0.063) and SDR was ($P = 0.01$; 95% CI: −0.11, −0.015). However, the mean umbilical arteries PI and RI were not significantly different between subjects and the controls.

Conclusion: There were statistically higher uterine artery impedance indices in the third trimester among singleton pregnant women with AMP than controls. This study also showed that the uterine artery impedance indices increased with the severity of malaria parasitemia.

Key words: Asymptomatic malaria parasitemia; Doppler flowmetry; impedance; singleton gestation; umbilical artery; uterine artery.

Introduction

Malaria in pregnancy constitutes a key and profound health problem in the malaria belt of the world. About half of the 50 million women who get pregnant in this zone annually are in the Sub-Saharan Africa where a significant proportion live in areas of high *Plasmodium falciparum* transmission.[1] The prevalence of malaria in pregnancy has been documented to be between 7.7% and 52.2% with a significant percentage being asymptomatic.[2-5]

Access this article online	
Website: www.tjogonline.com	Quick Response Code
DOI: 10.4103/TJOG.TJOG_5_18	

Address for correspondence: Dr. Ademola Joseph Adekanmi, Department of Radiology, College of Medicine, University of Ibadan, Ibadan, Nigeria.
E-mail: kanmiademola@gmail.com

How to cite this article: Adelodun AM, Adekanmi AJ, Roberts A, Adeyinka AO. Effect of asymptomatic malaria parasitemia on the uterine and umbilical artery blood flow impedance in third-trimester singleton Southwestern Nigerian pregnant women. Trop J Obstet Gynaecol 2018;35:333-41.

Asymptomatic malaria parasitemia (AMP) in pregnancy is the existence of malaria parasites in peripheral blood film of pregnant women without clinical symptoms.[6] It accounts for a significant percentage of malaria parasitemia in pregnancy in Sub-Saharan Africa where malaria transmission is high, with a prevalence of 48%–89%[3-8] in pregnancy with a prevalent rate of 22%–25.5% particularly in the third trimester of pregnancy.[7,8] AMP in pregnancy has been linked with low-level parasitemia but incredibly higher gametocyte carriage.[9] Due to the asymptomatic status, affected pregnant women are ignored, undetected, and untreated. However, pregnant women in this category present with almost the same maternal and fetal complications of overt malaria in pregnancy.[8-11] These include miscarriages, preterm labor/delivery, maternal anemia, low birth weight, intrauterine growth restriction, and intrauterine fetal demise.[8,10,11]

Malaria parasitemia in pregnancy is more severe in primigravidas due to low acquired immunity to malaria parasitemia with significant effects on the fetuses than in multigravidas,[12,13] with significant effects on uteroplacental and fetoplacental circulations with consequent fetal morbidities and mortalities.[14,15]

Doppler interrogation of the uterine and umbilical arteries among other investigative modalities is a crucial tool that has been utilized in the study of uteroplacental and fetoplacental abnormalities.[15,16] Doppler ultrasound of the umbilical and uterine arteries has evolved as the imaging modality of choice for the assessment of vascular hemodynamic changes in both normal and malaria-infected pregnant women due to its affordability, availability, and safety in pregnancy.[17,18]

The Doppler parameters evaluated in obstetrics to access vascular hemodynamics are as follows: end diastolic velocity (EDV), peak systolic velocity, pulsatility index (PI), resistance index (RI), and systolic to diastolic ratio.[19] However, the RI and PI are the commonly employed parameters in vascular flow study in malaria parasitemia in pregnancy.[14-16] Despite the high prevalence of malaria parasitemia in pregnancy and its associated complications, there is a knowledge gap on uterine and umbilical artery Doppler ultrasound vascular flow dynamics in AMP in pregnancy in our environment.

This research, therefore, studied the uterine and umbilical artery vascular flow hemodynamic changes in our women with AMP in the third trimester of singleton pregnancies using Doppler ultrasonography. Correlations between the uterine and umbilical arteries Doppler parameters (PI and RI) with gravidity and malaria parasite density among the study population were also evaluated.

Materials and Methods

Study design and setting

This was a prospective case–control study conducted at the ultrasound suite of the Radiology Department and the antenatal clinic (ANC) of University College Hospital Ibadan and a major referral center in Southwestern Nigeria. The study was conducted between June 2016 and January 2017 when the transmission was expected to be high.

Study population

Asymptomatic, singleton pregnant women with gestational age (GA) range of 28–38 weeks and whose blood film showed positive malaria parasitemia on microscopy without any clinical symptom were recruited for the study. The controls were asymptomatic, singleton pregnant women with negative malaria parasitemia attending the same ANC of our health institution.

The sample size was calculated using the formula for the comparison of means between two groups.[20] Using the standard deviation of the outcome variable of 0.089 by Griffin *et al*.[14] and allowing for 10% nonresponse, a sample size of 135 participants for cases were enrolled. Recruitment was based on the ratio of one subject to one control. A total of 270 participants were recruited.

Inclusion criteria were healthy pregnant women (singleton gestation) with GA range from 28 to 38 weeks regardless of gravidity, without symptoms of malaria, but showing malaria parasitemia on microscopy.

Exclusion criteria for cases were pregnant women; with GA below 28 weeks and over 38 weeks, those with malaria symptoms, for example, fever (temperature >37.5°C), headache, body/joint pain, body weakness, those diagnosed with hypertension/diabetes, hypertensive/diabetes medications, vascular disorders, Human immunodeficiency virus (HIV), sickle cell disease (SCD), or any other medical conditions. Others were multiple gestation, ultrasound diagnosed fetal malformations and nonconsenting pregnant women.

The controls were healthy pregnant women (singleton gestation) with GA range from 27 weeks to 38 weeks regardless of gravidity with neither malaria symptoms nor parasitemia on microscopy.

Controls that their GA were below 28 weeks and over 38 weeks. Those with hypertension/diabetes or on medications for hypertension/diabetes, HIV, SCD, vascular disorders, or other medical disorders were all excluded from the study.

Clinical evaluation

Consenting pregnant women who satisfied the inclusion criteria were recruited consecutively as well as their GA-matched controls. Their baseline data (sociodemographics) were obtained from the participants and or case file and recorded on a prepared data sheet. The axillary temperature of all the recruited pregnant women was checked with a digital thermometer and recorded. Blood pressure was done using Accoson mercury sphygmomanometer. Pulse rate was also noted. All to rule out clinical signs of fever and pregnancy-induced hypertension.

The actual GA at recruitment were estimated from the first trimester ultrasound. Otherwise, dating by the last menstrual period was used and confirmed for inclusion by obstetric ultrasound.

Laboratory evaluation

Malaria parasitemia was determined by microscopy. Finger-prick blood samples were collected on a clean slide, to make thick and thin films, from consenting participants. An experienced laboratory scientist prepared the slides using acetone, Giemsa's staining and air-drying. Each slide was examined by the same laboratory scientist under the light microscope using X1 oil immersion objective. A positive slide was the one that showed the presence of any asexual blood stages of Plasmodium species.

Parasite density per microliter was calculated by counting the number of parasites per 200 white blood cells on a thick blood film. The total white blood cell count estimate of 8000/μl was used.[21] Parasite density = Number of asexual stages × 8000 leukocytes/200 leukocytes.

The parasite density was graded as mild, moderate, and severe when the counts were between 1 and 999 parasite/μl, 1000–9999/μl, and >10,000/μl, respectively.[7,22]

Doppler ultrasound evaluation

Transabdominal color and pulsed Doppler ultrasound examination of the uterine and umbilical arteries (uteroplacental and fetoplacental circulation, respectively) was done on all the participants using an Ultrasonix SP ultrasound machine with a 3–5MHz curvilinear transducer.

Consenting patients were placed in a semi-recumbent position with a slight lateral tilt to avoid the development of supine hypotension from inferior vena cava compression. Patients were then exposed from the xiphisternum to the level of the groin hairline. Coupling gel was then applied to the skin.

The uterine artery was located transabdominally by placing the transducer longitudinally in the lower lateral quadrant of the abdomen with slight medial angulation.[19] Color Doppler imaging was then used to identify the uterine artery as it was seen crossing the external iliac artery.[23] The wall filter was kept at low value (50–60 Hz), and the angle of insonation was below 20°. Pulsed wave Doppler with a gate size of 2 mm was placed over it at about 1 cm below the crossover point[19] to generate the wave pattern [Figure 1a]. The PI and RI were automatically generated or manually traced when necessary. The values of 3 consecutive waveform were averaged and the mean recorded. Waveform abnormalities were also noted.

The umbilical artery was located by B-mode ultrasonography of the free loop of the umbilical cord using Color Doppler interrogation.[19] Following the same procedure for uterine artery, spectral waveforms were generated [Figure 1b]. Automatic tracing/manual tracing of the waveforms was done to generate the Doppler parameters. These parameters were recorded. Abnormalities such as low EDV, absent EDV, and reversal of flow were recorded.

Data management

The data collected were inputted and analyzed using statistical package for social sciences version 23.0. (Armonk, NY, IBM

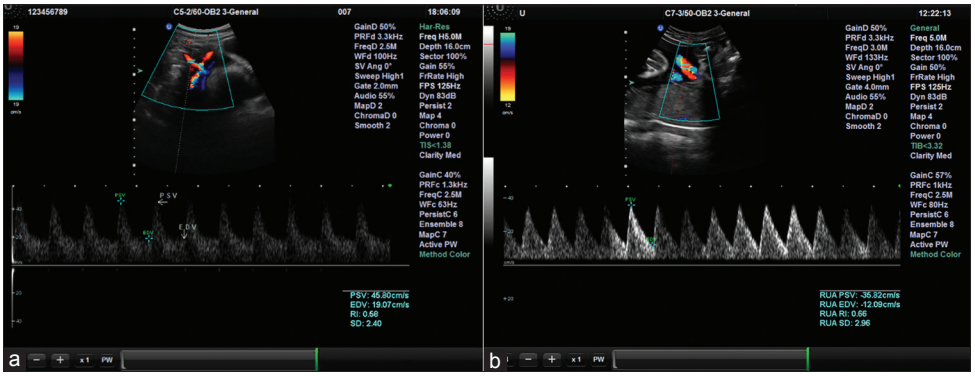

Figure 1: (a and b) Color and duplex Doppler ultrasound demonstrating the uterine waveform (a) and the characteristic saw tooth appearance of the umbilical artery (b) with the peak systolic velocity and the end-diastolic velocity demonstrated

Corp). The results obtained were presented using frequency tables, percentages, charts, graphs, means ± standard deviation as necessary. Chi-square was used to compare the sociodemographic characteristics of the study population. Independent student *t*-test was used to compare the mean Doppler velocimetric indices of the uterine and umbilical arteries of the AMP and control groups. ANOVA was used to test the relationship between Doppler velocimetric indices, increasing gravidity and malaria parasite density in participants with AMP at 5% level of significance, respectively. Scatter plot diagrams were used to show the relationship between the uterine and umbilical arteries Doppler indices and increasing GA.

Results

The demographic parameters of the 270 participants were as reported in Table 1. Majority of the AMP group (77%) were multigravida while 69% of the control group were multigravida. Most (57%) of the AMP group (cases) had mild malaria parasite density grading while 37.1% and 5.9% had moderate and severe malaria parasite density grading, respectively [Figure 2].

Uterine artery Doppler indices in the study population

The uterine artery mean PI and RI were higher in participants with AMP (PI = 0.85 ± 0.16 and RI; 0.59 ± 0.11), than controls (PI 0.77 ± 0.09 and RI = 0.51 ± 0.06). The mean difference between the groups were statistically significant PI = ($P < 0.001$; 95% confidence interval [CI] −0.11, −0.051) and RI = ($P < 0.001$; 95% CI −0.10, −0.063).

However, the umbilical arteries' mean Doppler PI and RI, between AMP cases and controls though higher in the former, were not significantly different [Table 2].

There was a gradual reduction in the mean uterine artery PI as gravidity increases. The values 0.93 ± 0.18, 0.85 ± 0.16, 0.84 ± 0.15, 0.70 ± 0.09, and 0.69 ± 0.08 for Gravida 1, 2, 3, 4, and 5, respectively, showed statistically significant mean difference: F (4, 15) =8.86, $P = 0.001$. A similar trend to that of the PI was also noted in the uterine artery RI.

However, the umbilical artery showed an inconsistent and insignificant reduction in the mean of the PI and RI as gravidity increases as shown in Table 3.

Table 4 shows the relationship between Doppler velocimetric indices of the uterine and umbilical arteries in participants with AMP and malaria parasite density grading.

Table 1: Sociodemographics characteristics (age and gestational age distribution) of the participants

Variables	Pregnancy with AMP (n=135)		Normal pregnancy (n=135)		*P*
	$\bar{X}$±SD	Range	$\bar{X}$±SD	Range	
Age (years)	31.19±4.41	23-2	30.89±4.73	19-41	0.595
GA (weeks)	32.67±3.36	27-8	32.67±3.36	27-38	1.000
Gravidity	**Pregnancy with AMP**		**Normal pregnancy**		$\chi 2$ *P*
One	31 (23.0)		41 (30.4)		2.856 0.582
Two	47 (34.8)		44 (32.6)		
Three	43 (31.9)		35 (25.9)		
Four	11 (8.1)		10 (7.4)		
Five	3 (2.2)		5 (3.7)		

SD, Standard deviation; $\bar{X}$, Mean; *P* value significant at <0.05; ( ), Percentages and GA, Gestational age; AMP, Asymptomatic malaria parasitemia

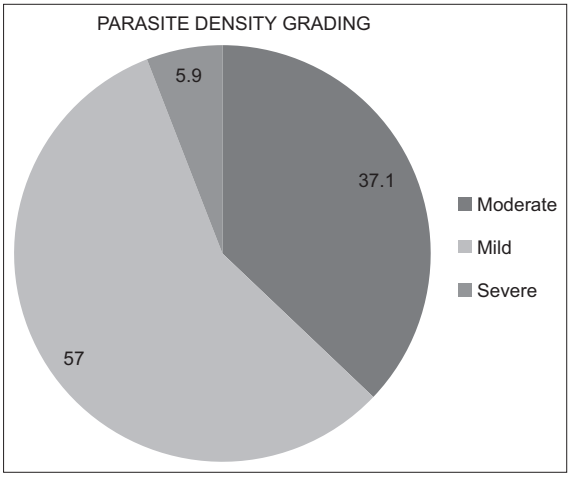

Figure 2: Malaria parasite density grading among cases

Table 2: Comparison of the mean Doppler velocimetric indices of the uterine and umbilical arteries of the asymptomatic malaria parasitemia and control groups

Outcome	Group, $\bar{X}$±SD		95% CI for mean difference	*t*	df	*P*
Doppler indices	**Pregnancy with AMP (n=135)**	**Normal pregnancy (n=135)**				
Uterine artery PI	0.85±0.16	0.77±0.09	−0.11-−0.051	−5.14	202	<0.001
Uterine artery RI	0.59±0.11	0.51±0.06	−0.10-−0.063	−8.02	201	<0.001
Umbilical artery PI	0.87±0.12	0.87±0.12	−0.034-0.023	−0.36	268	0.719
Umbilical artery RI	0.59±0.07	0.60±0.05	−0.008-0.023	0.914	246	0.362

SD, Standard deviation; $\bar{X}$, mean; *P* value significant at <0.05; PI, Pulsatility index; RI, Resistivity index and *t*, Student *t*-test; CI, Confidence interval; AMP, Asymptomatic malaria parasitemia

Table 3: Relationship between Doppler indices of uterine and umbilical arteries in participants with asymptomatic malaria parasitemia and gravidity

Variables	Parasite density grading, $\bar{X}\pm SD$			df1	df2	*F*	*P*	Tukey HSD
	Mild (*n*=77)	Moderate (*n*=50)	Severe (*n*=8)					
Uterine artery PI	0.75±0.09	0.97±0.15	1.03±0.16	2	18	47.08[a]	<0.001	1<2, 1<3
Uterine artery RI	0.53±0.06	0.68±0.10	0.68±0.07	2	19	51.66[a]	<0.001	1<2, 1<3
Umbilical artery PI	0.86±0.12	0.88±0.11	0.91±0.14	2	32	0.71	0.496	
Umbilical artery RI	0.58±0.07	057±0.05	0.75±0.06	2	32	29.11	<0.001	1<3, 2<3

[a]Asymptotically *F* distributed. df, degree of freedom; $\bar{X}$, Mean; SD, Standard deviation and *P* value significant at <0.05; PI, Pulsatility index; RI, Resistivity index; HSD, Honestly significant difference

The mean difference of the uterine artery PI between mild parasitemia (0.75 ± 0.09), moderate (0.97 ± 0.15), and severe (1.03 ± 0.16) were statistically significant: F (2, 18) =47.08, $P < 0.001$. Tukey's honestly significant difference (HSD) tests showed that the mean difference for both moderate and severe cases was statistically significantly higher than in the mild cases. However, the mean difference for moderate and severe cases did not differ significantly.

Furthermore, the mean difference of the uterine artery RI between mild parasitemia (0.53 ± 0.06), moderate (0.68 ± 0.10) and severe (0.68 ± 0.16) were statistically significant: F (2, 19) =51.66, $P < 0.001$. Tukey's HSD tests showed that the mean difference for both moderate and severe cases was significantly and statistically higher than in the mild cases. However, the mean difference for moderate and severe cases did not differ significantly.

In the umbilical artery, although the difference in mean PI between mild parasitemia (0.86 ± 0.0.12), moderate (0.88 ± 0.11) and severe (0.91 ± 0.14) were not statistically significant: F (2, 32) =0.71, $P = 0.496$. The mean difference of the umbilical artery RI between mild parasitemia (0.58 ± 0.07), moderate (0.57 ± 0.05) and severe (0.75 ± 0.06) were statistically significant: F (2, 32) =29.11, $P < 0.001$. Furthermore, Tukey's HSD tests showed that the mean difference for both mild and moderate cases was significantly and statistically lower than severe cases. However, the mean difference for mild and moderate cases did not differ significantly [Table 5].

Doppler indices and gestational age

The comparison of uterine and umbilical arteries Doppler indices between AMP and control groups at different GA showed that the uterine artery PI was higher in the AMP group than in the control group except at 35th and 38th weeks. The difference in mean between the two groups were statistically significant at 27th, 28th, 30th, 31st, and 32th weeks ($P = 0.015$, 0.001, 0.008, 0.048, and <0.001, respectively) [Table 4a].

Table 4a: Comparison of uterine artery Doppler indices between asymptomatic malaria parasitemia and control groups at different gestational age

GA (weeks)	*n*	Average uterine artery PI, $\bar{X}\pm SD$			Average uterine artery RI		
		AMP	Normal	*P*	AMP	Normal	*P*
27	9	0.99±0.13	0.85±0.06	0.015	0.60±0.09	0.56±0.05	0.281
28	10	1.06±0.16	0.82±0.07	0.001	0.67±0.08	0.53±0.39	<0.001
29	12	0.90±0.16	0.83±0.07	0.155	0.73±0.13	0.55±0.05	0.001
30	11	0.95±0.18	0.77±0.05	0.008	0.64±0.11	0.53±0.04	0.012
31	10	0.82±0.16	0.70±0.05	0.048	0.59±0.12	0.49±0.04	0.023
32	13	0.91±0.10	0.77±0.06	<0.001	0.59±0.11	0.47±0.06	0.003
33	10	0.85±0.17	0.80±0.05	0.340	0.59±0.09	0.51±0.04	0.029
34	12	0.84±0.14	0.79±0.09	0.357	0.57±0.07	0.53±0.04	0.124
35	13	0.77±0.08	0.80±0.09	0.420	0.57±0.07	0.53±0.05	0.095
36	14	0.77±0.12	0.73±0.05	0.287	0.60±0.08	0.49±0.05	<0.001
37	12	0.72±0.06	0.69±0.11	0.427	0.51±0.05	0.49±0.07	0.305
38	9	0.68±0.08	0.71±0.06	0.394	0.48±0.06	0.48±0.03	0.921

SD, Standard deviation; $\bar{X}$, Mean; *P* value significant at <0.05; PI, Pulsatility index; RI, Resistivity index and GA, Gestational age; AMP, Asymptomatic malaria parasitemia

Table 4b: Comparison of umbilical artery Doppler indices between asymptomatic malaria parasitemia and control groups at different gestational age

GA (weeks)	*n*	Average umbilical artery PI, $\bar{X}\pm SD$			Average umbilical artery RI, $\bar{X}\pm SD$		
		AMP	Normal	*P*	AMP	Normal	*P*
27	9	1.01±0.14	0.98±0.10	0.599	0.68±0.06	0.64±0.04	0.110
28	10	1.03±0.12	1.00±0.09	0.631	0.67±0.08	0.65±0.03	0.448
29	12	1.02±0.12	0.96±0.15	0.284	0.60±0.04	0.62±0.06	0.372
30	11	0.82±0.07	0.87±0.04	0.067	0.58±0.07	0.60±0.04	0.396
31	10	0.86±0.04	0.83±0.06	0.134	0.57±0.04	0.59±0.03	0.170
32	13	0.90±0.06	0.92±0.05	0.360	0.59±0.07	0.62±0.02	0.176
33	10	0.90±0.07	0.91±0.04	0.819	0.60±0.06	0.63±0.02	0.200
34	12	0.79±0.06	0.85±0.08	0.051	0.61±0.05	0.58±0.06	0.218
35	13	0.80±0.08	0.84±0.09	0.251	0.58±0.04	0.59±0.02	0.641
36	14	0.85±0.05	0.83±0.09	0.671	0.53±0.07	0.55±0.06	0.251
37	12	0.81±0.07	0.74±0.09	0.058	0.56±0.07	0.58±0.05	0.362
38	9	0.72±0.07	0.70±0.05	0.365	0.53±0.08	0.51±0.05	0.533

SD, Standard deviation; $\bar{X}$, mean; *P* value significant at <0.05; PI, Pulsatility index; RI, Resistivity index and GA, Gestational age; AMP, Asymptomatic malaria parasitemia

The uterine artery PI showed significant negative correlation (*r*) with increasing GA in both AMP and control groups ($r = -0.594, P < 0.001$) and ($r = -0.404, P < 0.001$) respectively [Figure 3a and b].

The uterine artery RI was also higher in the AMP group than in the control group except at 38th week. The difference in mean between the two groups was statistically significant at 28th, 29th, 30th, 31st, 32th, 33th, and 36th weeks ($P \leq 0.001$, 0.001, 0.012, 0.023, 0.003, 0.029, and <0.001, respectively) [Table 4a]. Furthermore, the uterine artery RI showed a negative correlation (r) with increasing GA in both AMP and control groups with statistically significant values. ($r = -0.450, P < 0.001$) and ($r = -0.318, P < 0.001$), respectively [Figure 4a and b].

The Doppler indices in the umbilical artery at different GA showed that there was no statistically significant mean PI and RI difference between the AMP and the control groups at any of the GAs [Table 4b]. However, the umbilical artery PI showed statistically significant negative correlation with increasing GA in both AMP and control groups. ($r = -0.629, P < 0.001$) and ($r = -0.631, P < 0.001$), respectively. Furthermore, the umbilical artery RI showed a negative correlation of the RI with increasing GA in both AMP and control groups with statistically significant values ($r = -0.473, P < 0.001$) and ($r = -0.554, P < 0.001$), respectively.

No uterine spectral waveform abnormality like early diastolic notching was noted in both AMP and control groups. The umbilical spectral waveform also shows no absent end-diastolic volume or reversal of flow in the two groups.

Discussion

Doppler velocimetry of the uterine and umbilical arteries is an important tool for the assessment of changes in the utero-placenta and feto-placenta circulation.[18] During a normal pregnancy, there is a continuous decrease in the

Table 5: Relationship between Doppler velocimetric indices of the uterine and umbilical arteries in participants with asymptomatic malaria parasitemia and malaria parasite density grading

Variables	Parasite density grading, $\bar{X} \pm SD$			df1	df2	*F*	*P*	Tukey HSD
	Mild ($n=77$)	Moderate ($n=50$)	Severe ($n=8$)					
Uterine artery PI	0.75±0.09	0.97±0.15	1.03±0.16	2	18	47.08[a]	<0.001	1<2, 1<3
Uterine artery RI	0.53±0.06	0.68±0.10	0.68±0.07	2	19	51.66[a]	<0.001	1<2, 1<3
Umbilical artery PI	0.86±0.12	0.88±0.11	0.91±0.14	2	32	0.71	0.496	
Umbilical artery RI	0.58±0.07	057±0.05	0.75±0.06	2	32	29.11	<0.001	1<3, 2<3

[a]Asymptotically *F* distributed. df, degree of freedom; $\bar{X}$, mean; SD, Standard deviation and *P* value significant at <0.05. PI, Pulsatility index; RI, Resistivity index; HSD, Honestly significant difference

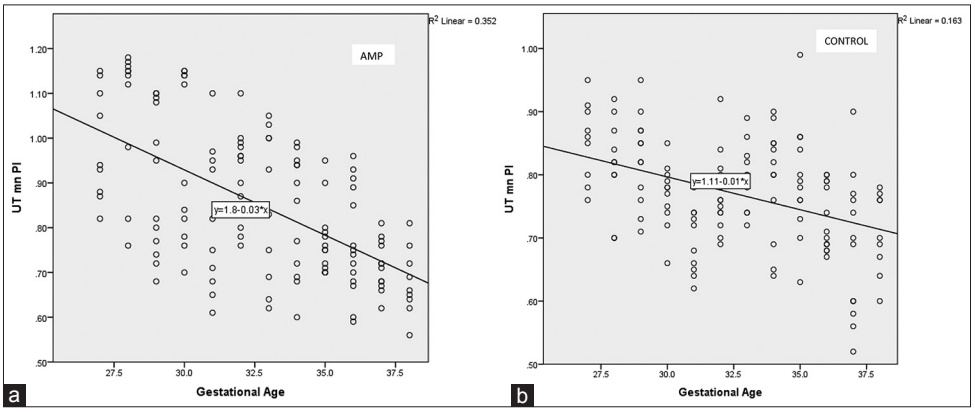

Figure 3: (a and b) Scatter plots of mean uterine artery pulsatility index against gestational age in both AMP and control groups, respectively

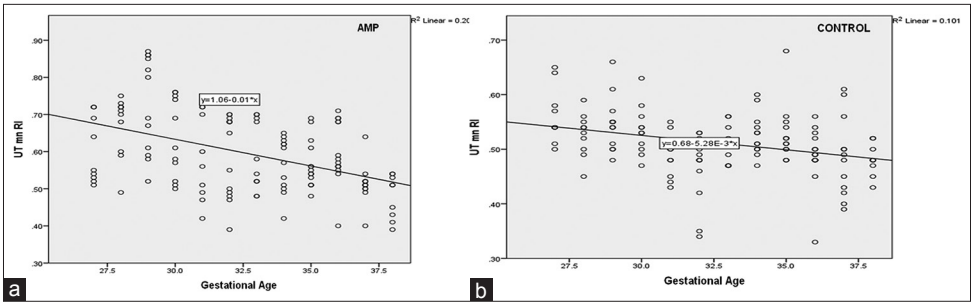

Figure 4: (a and b) Scatter plots of mean uterine artery resistive index against gestational age in both AMP and control groups, respectively

values of Doppler parameters in the uterine and umbilical arteries as GA advances due to trophoblastic extra-villous conversion of the uterine spiral arteries and multiplicity of the arterial channels of the placenta respectively.[24] However, studies have shown that overt malaria parasitemia in pregnancy causes elevated uterine and umbilical Doppler indices.[14,23-25] This is believed to be due to alteration of blood flow within the uterine and umbilical vessels from sequestration of Plasmodium-infected erythrocytes within the placenta tissue.

In this study, the mean age of the study population was 31.19 ± 4.41 years for the participants with AMP in pregnancy similar to 30.89 ± 4.73 years recorded for the controls. These mean ages of the participants are comparable to the study done by Aluko and Oluwatosin[26] in Ibadan on knowledge and utilization of malaria control measures by pregnant women and newly delivered mothers.

We observed that the mean uterine artery Doppler parameters (PI and RI) are significantly higher ($P > 0.001$ and $P > 0.001$, respectively) in the subjects with AMP in pregnancy when compared with the controls. This depicts increased vascular resistance in the uteroplacental circulation possibly from sequestrated erythrocytes within the placenta tissue. These findings are comparable to those of Griffin *et al*.[14] in Democratic Republic of Congo which showed that *P. falciparum* parasitemia increased uterine artery RI among primigravidae. And also in agreement with the report of Dorman *et al*.[15] in Kenya which revealed an abnormal uterine artery velocity waveform in pregnancies complicated by malaria. The similarities are likely due to the pathophysiological process of the disease condition.

In this study, the mean umbilical arteries Doppler parameters showed no significant difference between the subjects with AMP in pregnancy and the controls which may depict lack of vascular resistance probably from some level of acquired immunity at the level of fetoplacental circulation. Perhaps, this is protective of the developing fetus, although fetal outcome was not determined in this study. However, fetal outcomes may be different in cases of overt malaria. Our observation is in agreement with the report of Filho *et al*.[24] (Brazil) where no difference in umbilical PI and RI between the cases and controls were seen. Furthermore, Mcclure *et al*.[23] (Kenya) reported no difference in umbilical PI between cases and controls. These similarities in findings might be due to possible acquired immunity of the participants in both studies.

However, Mcclure *et al*.[23] and Dent *et al*.[25] both in Kenya reported a significantly higher umbilical RI and higher umbilical PI and RI, respectively, when compared with their controls which are not in agreement with this study. These studies were however carried out in pregnant women with overt malaria cases, and the attendant vascular changes of overt malaria might have contributed to the higher indices reported. It is also possible that this may also be due to the difference in the degree of acquired immunity to malaria parasitemia between the populations studied. The work of Dent *et al*.[25] was also carried out at 18–23 weeks of gestation, unlike the third trimester in this present study.

There was a gradual decline in the uterine arteries Doppler indices (PI and RI) of the participants with AMP in pregnancy and controls as GA increases. The umbilical artery also shows a fair declining trend. This observation is, however, less consistent in subjects with asymptomatic AMP in pregnancy than controls in the umbilical artery. This overall consistent decline is likely due to increase vascular resistance in the uteroplacental and fetoplacental circulation in the AMP group. At present, to the best of our knowledge, there is paucity of publication on the association between uterine and umbilical arteries Doppler indices of the participants with AMP in pregnancy and controls as GA increases hence the difficulty in comparing these with findings from other climes.

In this study, the uterine artery PI and RI in subjects with AMP in pregnancy showed a significant gradual decline as gravidity increases ($P = 0.001$ and $P < 0.001$, respectively). This denotes a reduction in the vascular resistance of the uteroplacental circulation as gravidity increases and may be attributable to increase in the level of acquired immunity as gravidity increases from the increased level of antibodies against malaria parasitemia. These findings are comparable to that of Griffin *et al*.[14] in Democratic Republic of Congo. They reported that malaria increased uterine artery RI by 11%–13% among primigravidas but did not increase uterine artery RI among multigravidas. This is likely due to the endemicity of malaria parasitemia in both study population leading to increased level of acquired immunity as gravidity increases.

Contrary to that of the uterine arteries, the umbilical artery Doppler PI and RI in subjects with AMP in pregnancy showed no significant changes as gravidity increases. This may be attributable to the level of adaptive immunity to malaria parasitemia in the study locality. These findings are comparable to that of in French Guiana which reported that malaria-affected multipara and primipara umbilical Doppler parameters equally. These similarities in findings may be due to the endemicity of malaria parasitemia in both study population which likely account for the possible adaptive immunity as gravidity increases.

The uterine artery PI and RI values increase in AMP in pregnancy women than controls as parasite density increases ($P < 0.001$ and $P < 0.001$, respectively). We believe this may be attributable to increasing level of malaria-infected erythrocytes within the placenta tissue.

Again, there is a dearth of publication on the association between uterine artery Doppler indices of AMP in pregnancy and increased parasite density grading making comparison difficult.

In this study, the umbilical artery PI values in participants with AMP in pregnancy showed no significant changes as parasite density grading increases. These findings are similar to the report of Arbeille *et al*.[27] in French Guiana which showed no significant changes between umbilical artery Doppler indices and malaria parasite density grading. However, the umbilical artery Doppler RI values in subjects with AMP in pregnancy showed significant changes as parasite density increases.

Conclusion

The presence of AMP significantly causes high uteroplacental bed RI and PI in the third trimester, compared to the fetoplacental circulation. And these parameters (RI and PI), increases with increasing malaria parasite density. The widely reported adaptive immunity in malaria endemic zones probably confers protection to the fetus (fetoplacental circulation) in mild and moderate malaria parasitemia. However, severe malaria parasitemia, although asymptomatic is significantly associated with high RI the fetoplacental circulation.

There is a consistent decline in uterine RI and PI with increasing GA in third-trimester singleton pregnant women with AMP and controls.

A longitudinal study is recommended to follow-up and monitor the Doppler changes till delivery and to compare the Doppler findings with the fetal outcome.

Recommendation

Obstetric Doppler ultrasound, after a malaria parasite test, is recommended for healthy pregnant women with AMP, most especially in severe parasitemia. This will help in detecting those with high Doppler impedance indices which may indicate uteroplacental insufficiency, hence aiding early intervention.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ntirushwa D. A Strategic Framework for Malaria Prevention and Control During Pregnancy in the African Region. Brazzaville: WHO Regional Office for Africa; 2004. p. 1-38.
2. Agomo CO, Oyibo WA, Anorlu RI, Agomo PU. Prevalence of malaria in pregnant women in Lagos, South-West Nigeria. Korean J Parasitol 2009;47:179-83.
3. Falade CO, Olayemi O, Dada-Adegbola HO, Aimakhu CO, Ademowo OG, Salako LA, *et al.* Prevalence of malaria at booking among antenatal clients in a secondary health care facility in Ibadan, Nigeria. Afr J Reprod Health 2008;12:141-52.
4. Iriemenam NC, Dosunmu AO, Oyibo WA, Fagbenro-Beyioku AF. Knowledge, attitude, perception of malaria and evaluation of malaria parasitaemia among pregnant women attending antenatal care clinic in metropolitan Lagos, Nigeria. J Vector Borne Dis 2011;48:12-7.
5. Ojiezeh TI, Ibeh NI, Opedun DO, Udoh SJ. Malaria endemicity among pregnant women in urban and semi-urban areas in Southwest, Nigeria. Am Eurasian J Sci Res 2010;5:207-11.
6. Wilson NO, Bythwood T, Solomon W, Jolly P, Yatich N, Jiang Y, *et al.* Elevated levels of IL-10 and G-CSF associated with asymptomatic malaria in pregnant women. Infect Dis Obstet Gynecol 2010;2010. pii: 317430.
7. Nwagha UI, Ugwu VO, Nwagha TU, Anyaehie BU. Asymptomatic *Plasmodium* parasitaemia in pregnant Nigerian women: Almost a decade after roll back malaria. Trans R Soc Trop Med Hyg 2009;103:16-20.
8. Ogbu GI, Aimakhu CO, Anzaku SA, Ngwan S, Ogbu DA. Prevalence of malaria parasitaemia among asymptomatic women at booking visit in a tertiary hospital, Northcentral Nigeria. J Reprod Biol Health 2015;3:1.
9. Balogun ST, Adeyanju OA, Adedeji AA, Fehintola FA. Predictors of asymptomatic malaria in pregnancy. Niger J Physiol Sci 2011;26:179-83.
10. Nwali MI, Umeora OU, Ozumba BC, Onoh RC, Agwu UM, Agboeze J, *et al.* Outcomes of asymptomatic malaria parasitaemia in neonates in a tertiary hospital, Southeast Nigeria. Niger Med J 2014;55:250-3.
11. Bassey G, Nyengidiki TK, John CT. Prevalence of placenta *Plasmodium* parasitemia and pregnancy outcome in asymptomatic patients at delivery in a university teaching hospital in Nigeria. Niger J Clin Pract 2015;18:27-32.
12. Desai M, ter Kuile FO, Nosten F, McGready R, Asamoa K, Brabin B, *et al.* Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis 2007;7:93-104.
13. Akanbi OM, Odaibo AB, Afolabi K, Ademowo OG. Prevalence of malaria and anaemia in pregnancy in Ibadan, South-Western Nigeria. Niger J Parasitol 2004;25:51-5.
14. Griffin JB, Lokomba V, Landis SH, Thorp JM Jr., Herring AH, Tshefu AK, *et al. Plasmodium falciparum* parasitaemia in the first half of pregnancy, uterine and umbilical artery blood flow, and foetal growth: A longitudinal Doppler ultrasound study. Malar J 2012;11:319.
15. Dorman EK, Shulman CE, Kingdom J, Bulmer JN, Mwendwa J, Peshu N, *et al.* Impaired uteroplacental blood flow in pregnancies complicated by falciparum malaria. Ultrasound Obstet Gynecol 2002;19:165-70.
16. Everett TR, Lees CC. Beyond the placental bed: Placental and systemic determinants of the uterine artery Doppler waveform. Placenta. 2012;33:893-901.
17. Derwig I, Lythgoe DJ, Barker GJ, Poon L, Gowland P, Yeung R, *et al.* Association of placental perfusion, as assessed by magnetic resonance imaging and uterine artery Doppler ultrasound, and its relationship to pregnancy outcome. Placenta 2013;34:885-91.
18. Mone F, Mc Auliffe FM, Ong S. The clinical application of Doppler ultrasound in obstetrics. Obstet Gynaecol 2015;17:13-9.
19. Bhide A, Acharya G, Bilardo CM, Brezinka C, Cafici D, Hernandez-Andrade E, *et al.* ISUOG practice guidelines: Use of Doppler ultrasonography in obstetrics. Ultrasound Obstet Gynecol 2013;41:233-39.

20. Kirkwood BB, Sterne J. Essential Medical Statistics. Malden, MA: Blackwell Science; 2003. p. 1-512.
21. World Health Organization. Basic Malaria Microscopy 2. Geneva: World Health Organization; 2010. Available from: http://www.whqlibdoc.who.int/publications/2010/9789241547826_eng.pdf. [Last accessed on 2018 Nov 16].
22. Nega D, Dana D, Tefera T, Eshetu T. Prevalence and predictors of asymptomatic malaria parasitemia among pregnant women in the rural surroundings of Arbaminch town, South Ethiopia. PLoS One 2015;10:e0123630.
23. McClure EM, Meshnick SR, Lazebnik N, Mungai P, King CL, Hudgens M, *et al.* A cohort study of *Plasmodium falciparum* malaria in pregnancy and associations with uteroplacental blood flow and fetal anthropometrics in Kenya. Int J Gynaecol Obstet 2014;126:78-82.
24. Machado Filho AC, da Costa EP, da Costa EP, Reis IS, Fernandes EA, Paim BV, *et al.* Effects of vivax malaria acquired before 20 weeks of pregnancy on subsequent changes in fetal growth. Am J Trop Med Hyg 2014;90:371-6.
25. Dent A, Lazebnik N, Gisemba E, Kalayjian B, Muchiri E, Bohine LC. Fetal biometrics, umbilical and uterine Doppler studies among malaria infected and not infected pregnant women. Ultrasound Obstet Gynaecol 2011;38:130.
26. Aluko JO, Oluwatosin AO. Utilization of insecticide treated nets during pregnancy among postpartum women in Ibadan, Nigeria: A cross-sectional study. BMC Pregnancy Childbirth 2012;12:21.
27. Arbeille P, Carles G, Bousquet F, Body G, Lansac J. Fetal cerebral and umbilical artery blood flow changes during pregnancy complicated by malaria. J Ultrasound Med 1998;17:223-9.