Original Article

Comparison of flow-mediated dilation (FMD) of the brachial artery in normotensive versus preeclamptic pregnant females

Manju L. Verma, Namra Mueed, Uma Singh, Rekha Sachan, Pushp L. Sankhwar

Department of Obstetrics and Gynaecology, KGMU, Lucknow, Uttar Pradesh, India

Abstract

Introduction: Flow-mediated dilation (FMD) of the brachial artery is an ultrasonography test that assesses the endothelial response to reactive hyperemia. The aim of this study was to assess the changes in FMD in preeclamptic pregnant patients and compare them with normotensive pregnant females. **Methods:** An analytical cross-sectional comparative study was conducted in the Department of Obstetrics and Gynaecology at King George's Medical University (KGMU) after obtaining ethical approval. A total of 110 normotensive and 100 preeclamptic patients were recruited for the study. Using a Toshiba Ultrasound Machine with a 7–12 MHz probe, the baseline diameter of the brachial artery D1 was measured. Afterward, the cuff of the sphygmomanometer was placed distally on the forearm and it was inflated up to ≥250 mm of Hg pressure and later slowly deflated. At 90th seconds after cuff deflation, the mean of three measurements of vessel caliber (D2) was obtained. The FMD% was obtained by the following equation: FMD (%) = [(D2 − D1)/D1] ×100, where D1 = basal diameter and D2 = post-occlusion diameter. All patients were followed till delivery for maternofetal outcome. **Results:** FMD% was significantly lower in the preeclampsia group, and it went on decreasing with increasing severity of preeclampsia. At the cutoff of 9.4 for FMD%, its sensitivity for the prediction of preeclampsia was 65.3%, specificity was 89.3%, positive predictive value (PPV) was 94%, and negative predictive value (NPV) was 50%. **Discussion:** FMD is a noninvasive test, and it gets decreased before clinical signs of preeclampsia, so it can be used as a predictor of preeclampsia.

Keywords: Flow-mediated dilation, hypertension of pregnancy, preeclampsia

Introduction

Preeclampsia is a hypertensive disease associated with pregnancy with multisystem involvement. It is an important cause of increased maternal and fetal morbidity and mortality if not diagnosed in time and managed well. Many pregnant women seek first medical advice from primary care providers, so it is important that primary care providers must be aware of preeclampsia, its implications, and newer developments related to the disease. It is a disorder of vascular endothelial function and vasospasm that appear after 20 weeks of gestation and can present as late as 4–6 weeks postpartum. Endothelial function can be assessed using flow-mediated dilation (FMD) of the brachial artery, which is an ultrasonography test that assesses the endothelial response to reactive hyperemia.[1] FMD is a well-established technique that allows researchers to examine endothelial function and assess cardiovascular risk noninvasively, even during pregnancy.[2,3] This technique offers possibilities to examine how endothelial dysfunction contributes to the pathophysiology of preeclampsia.

Address for correspondence: Dr. Manju L. Verma, Department of Obstetrics and Gynaecology, KGMU, Lucknow, Uttar Pradesh, India.
E-mail: gaganmlv@gmail.com

Received: 09-05-2023 **Revised:** 08-12-2023
Accepted: 21-12-2023 **Published:** 24-05-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_773_23

How to cite this article: Verma ML, Mueed N, Singh U, Sachan R, Sankhwar PL. Comparison of flow-mediated dilation (FMD) of the brachial artery in normotensive versus preeclamptic pregnant females. J Family Med Prim Care 2024;13:1863-7.

The aim of this study was to assess the FMD of the brachial artery in normotensive and preeclamptic pregnant women.

Material and Methods

This analytical cross-sectional comparative study was conducted in the Department of Obstetrics and Gynaecology, King George's Medical University (KGMU), Lucknow, for one year. This study obtained approval from the Institutional Ethics Committee, KGMU, Lucknow, Ref. Code: 92nd P/29. The study population comprised two groups.

The first group comprised normotensive (blood pressure (BP) <130/90 mmHg) pregnant females, and group B comprised preeclamptic pregnant females.

For preeclampsia diagnosis, the following criteria have been used in the study as per the American College of Obstetricians and Gynecologists (ACOG) guideline.

Elevation of the arterial pressure after 20 weeks of gestational age (systolic BP (SBP) ≥140 or diastolic BP (DBP) ≥90 mmHg) observed at two measurements with a 4-hour interval.

Proteinuria (1+ or above at proteinuria tape or 24-h proteinuria >0.3 g/24 h) with or without signs or symptoms observed.

Preeclampsia with severe feature: SBP ≥160 or DBP ≥110 mmHg observed at two measurements with a 4-hour interval.

Thrombocytopenia <1,00,000/ul.

Impaired liver function (twice that of normal).

Severe persistent right upper quadrant pain or epigastric pain.

Progressive renal insufficiency.

New-onset cerebral or visual disturbances.

With/without proteinuria.

Inclusion criteria

Age 18–45 years.

Normotensive and preeclamptic patients (20–40 weeks of gestation) were enrolled in the study.

Patient willing to participate in the study.

Exclusion criteria

H/O hypertension/diabetes before gestation or nonsteroidal anti-inflammatory drug (NSAID) abuse.

H/O autoimmune disease and antiphospholipid antibodies (APLA).

Known c/o chronic kidney disease (CKD), cardiovascular disorder (CVD), and vascular disorder.

The patient is not willing to participate in the study.

This was an analytical cross-sectional study in which FMD% was compared between the two groups. The sample size of the study was 200 pregnant women, comprising 100 pregnant women with preeclampsia and 100 normotensive females. This was determined using the minimum number of females per group required for the study using the standard formula for sample size in a comparative study and setting the study power at 90%. To derive our sample size, we used data from a previously published study about variation in FMD% in preeclamptic pregnant females. Written informed consent to participate in the study was obtained from each woman. All women who fulfilled the inclusion criteria and gave consent were subjected to a detailed personal history and obstetrical history. After 20 weeks, 100 normotensive (group 1) and 100 preeclamptic (group 2) women were enrolled. The FMD technique was performed with a Toshiba Doppler ultrasonography machine with a 7–12 MHz linear transducer. Before the scan, the patient was placed at rest for 15 minutes in a dorsal decubitus position. The blood pressure of the patient was measured, and her brachial artery was identified medially in the antecubital fossa of the dominant upper limb. An image of the vessel was obtained at approximately 5 cms above the elbow in the longitudinal section (B mode) during the minimum distention of the vessel corresponding to the cardiac diastole. The image was frozen to obtain the average of three measurements of vessel caliber (from anterior to posterior walls of tunica media–adventitia interface) (D1), which was the baseline diameter of the brachial artery. After obtaining the baseline diameter of the brachial artery (D1), the cuff of the sphygmomanometer was placed distally on the forearm and it was inflated up to ≥250 mm of Hg pressure and later slowly deflated. At 90th seconds after cuff deflation, the mean of three measurements of vessel caliber (D2) was obtained. The FMD% was obtained by the following equation:

FMD (%) = [(D2 − D1)/D1] ×100, where D1 = basal diameter and D2 = post-occlusion diameter. All patients were followed till delivery, and maternofetal outcome was noted. In maternal outcome, the period of gestation for termination and the mode of delivery were noted. For fetal outcome birth weight, the need for neonatal intensive care unit (NICU) and neonatal unit (NNU) admission was noted. The data were expressed as mean and standard deviation (SD) or median, range, and percentage as appropriate. All the categorical data are compared using the Chi-square test. Continuous variables in two groups were compared by *t*-test. More than two variables were analyzed by one-way analysis of variance (ANOVA), followed by Tukey's *post hoc* test. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used for diagnosing

preeclampsia by FMD. The *P* value of < 0.05 was considered significant. The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) 26.0 version (Chicago, Inc., USA) Windows software.

Results

In group 2 of 100 patients, 58 had nonsevere preeclampsia (group IIa) and 42 had severe preeclampsia (group IIb). Table 1 shows a comparison of hemodynamic status in both groups. Table 2 illustrates that FMD% was significantly lower in the preeclampsia group, and it went on decreasing with increasing severity of preeclampsia. In the normotensive group, FMD% was 12.2, while it was 10.22 in the non-severe preeclampsia group, which was further reduced to 8.7 in the severe preeclampsia subgroup. Table 3 shows the intragroup comparison of FMD in two groups. Tables 4 and 5 and Figure 1 show the good PPV of FMD for the prediction of preeclampsia. At a cutoff of 9.4 for FMD, it has a PPV of 94%. Table 6 shows an overview of gestation at termination and a comparison of fetal outcomes.

Discussion

The present study concluded that flow-mediated dilation of the brachial artery can be used for the prediction of preeclampsia. The capacity for blood vessel dilation is necessary for healthy gestation, and when it is absent, the maternal and fetal prognosis is compromised. While calculating the FMD of the brachial artery, the mean baseline luminal diameter was less in the preeclamptic group than in the normotensive group; however, this difference was not statistically significant between the two groups, whereas mean FMD after the release of compression at 90th seconds and FMD% were significantly different between the two groups. The mean FMD in group I after the release of compression at 90th seconds and FMD%, respectively, were 2.91 ± 0.36 and 12.25 ± 2.19, and the mean FMD in group II after the release of compression at 90th seconds and FMD%, respectively, were 2.75 ± 0.35 and 9.59 ± 2.06 ($P < 0.001$). This can be explained by the fact that the capacity of blood vessel dilation is increased in normal healthy pregnant women with increasing gestation due to increasing levels of vasodilator substance (such as nitric oxide) in the blood, while

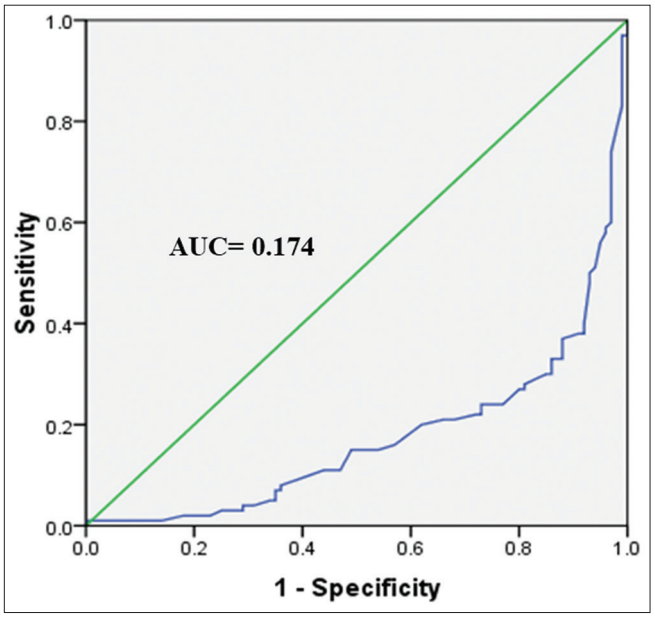

Figure 1: Receiver operating characteristic (ROC) curve analysis for the diagnosis of preeclampsia. Each receiver's characteristic curve is expressed as a solid line. AUC: area under the curve

Table 1: Comparisons of hemodynamic status of the patients in group I, group IIa, and group IIb

	Group I (*n*=100)	Group IIa (*n*=58)	Group IIb (*n*=42)	[1]*P*
Systolic blood pressure (mmHg)	120.95±9.26	142.17±5.42	157.17±11.01	<0.001*
Diastolic blood pressure (mmHg)	76.04±7.53	91.69±3.36	104.21±7.06	<0.001*
MAP (mmHg)	91.01±7.56	108.52±2.69	121.87±7.51	<0.001*

Table 2: Comparison of flow-mediated dilation (FMD) among group I, group IIa, and group IIb patients

	Group I (*n*=100)	Group IIa (*n*=58)	Group IIb (*n*=42)	[1]*P*
Baseline luminal diameter	2.60±0.33	2.52±0.32	2.49±0.32	0.149
After the release of compression at 90 sec	2.91±0.36	2.78±0.35	2.71±0.34	0.003*
FMD%	12.25±2.19	10.22±2.22	8.71±1.41	<0.001*

SD=Standard deviation, [1]ANOVA, *Significant

Table 3: Intragroup comparison (Tukey's post hoc) of flow-mediated dilation (FMD) in between group I, non-severe preeclampsia (group IIa), and severe preeclampsia (group IIb) patients

	Group I Vs group IIa		Group I Vs group IIb		Group IIa Vs group IIb	
	Mean difference	*P*	Mean difference	*P*	Mean difference	*P*
Baseline luminal diameter	0.07	0.372	0.11	0.175	0.04	0.857
After the release of compression at 90 sec	0.13	0.065	0.21	0.005*	0.08	0.540
FMD%	2.03	<0.001*	3.54	0.001*	1.51	0.001*

*Significant

in preeclampsia, due to preceding endothelial dysfunction, this phenomenon is failed, which leads to decrement in the value of FMD in the second half of pregnancy. This observation was supported by the Brandao AHF *et al.* (2012)[4] study, in which FMD was performed twice for a patient, first at 16–20 weeks and second at 24–28 weeks of gestational age. They found that the group of patients who did not develop preeclampsia had shown an increase in FMD (74.2 ± 184.2%) value, while the group of patients who developed preeclampsia had shown a decrease (16.6 ± 38.2%) in the value of FMD ($P = 0.003$). Bansal *et al.* (2016)[5] also showed that the mean FMD of women with preeclampsia was significantly lower than that of the normotensive group (6.14 ± 2.90% v/s 7.70 ± 1.81%, *P* value 0.027). Negin Rezavand *et al.* (2017)[6] had also similar results, and mean FMD values were 9.72%, 5.07%, and 4.33% in the healthy group, mild preeclampsia, and severe preeclampsia ($P < 0.001$), respectively, in their study.

Table 4: Sensitivity, specificity, positive productive value (PPV), and negative productive value (NPV) of diagnosing preeclampsia by flow-mediated dilation (FMD)

Test	Cutoff (median)	Sensitivity	Specificity	PPV	NPV
FMD	9.4	65.3%	89.3%	94.0%	50.0%

Table 5: Receiver operating characteristic (ROC) analysis of FMD in preeclampsia patients

	Area	Std. error	Significant	95% confidence interval	
				Lower bound	Upper bound
FMD	0.174	0.029	<0.001*	0.116	0.232

Table 6: Gestation weeks, mode of termination, and type of delivery and details of outcome baby in between group I and group II

Gestational age (weeks)	Group I (*n*=100)	Group II (*n*=100)	*P*
	38.01±3.23	36.90±4.31	0.042*
Mode of termination			
LSCS	33 (33.0%)	34 (34.0%)	0.881
VD	67 (67.0%)	66 (66.0%)	
Delivery			
Induced labor	42 (42.0%)	34 (34.0%)	0.338
Spontaneous	58 (58.0%)	67 (67.0%)	
Baby			
Weight	2.52±0.43	2.36±0.62	0.033*
Sex M/F	45/55	47/53	0.887
NNU/NICU	17 (17.0%)	27 (27.0%)	0.089

*Significant

Although in the present study, FMD could not be done in the postpartum period, Kuscu NK *et al.*[7] and Mori *et al.*[8] found that FMD increased by four to six weeks postpartum in women who had preeclampsia, suggesting a partial reversal of the endothelial dysfunction observed at diagnosis. However, Hamad RR *et al.*[9] and Goynumer G. *et al.*[10] suggest that FMD remains lower in women who had preeclampsia for up to 3 years postpartum. By utilizing a cutoff point of 9.4 (median), the FMD of the brachial artery for overall sensitivity, specificity, PPV, and NPV for the diagnosis of preeclampsia was 65.3%, 89.3%, 94%, and 50.0%, respectively. In the present study, Pearson's correlation coefficient (-0.533) of FMD was negatively correlated with preeclampsia. It was also found in a study that sensitivity and PPV increase with the severity of the disease from 75% to 82.2% and 88% to 97%. So, FMD of the brachial artery may be a promising screening tool for the prediction of preeclampsia, but a larger population cohort is required to confirm this observation.

A comparison of different study FMD% (mean cutoff value), sensitivity, specificity, PPV, and NPV for preeclamptic patients is shown as follows:

Kamat R *et al.*[11] depicted that the value of FMD% ranges around 1–9% in those women who had a 62% of risk developing hypertension when they measured FMD twice in pregnancy. Their range of FMD was found nearer to our study [Table 7]. The lower cutoff value of FMD% in other studies, such as Negin Rezavand *et al.*,[6] Calixto A.C. *et al.*,[12] and Oliveira OP *et al.*,[13] can be explained by the fact that they included only high-risk population, such as chronic arterial hypertension, pregestational diabetes mellitus (DM), personal history of preeclampsia in previous gestation, and family history of preeclampsia (mother or sister), while in recent study cases who had history of chronic hypertension, prepregnancy diabetes and previous history of preeclampsia were excluded because abovementioned

Table 7: Comparison of various previous studies and present study

Study	Year	Mean Fmd% value of preeclamptic Pt.	Sensitivity	Specificity	pPV	NPV
Kamat R *et al.*[11]	2011	9%	88%	93%	84%	94.8%
Brando AHF *et al.*[4]	2014	6.5%	84% (early-onset PET=75%) (late-onset PET=83.3%)	73.6% (early-onset PET=73%) (late-onset PET=73.3%)	45.7% (early-onset PET=32%) (late-onset PET=34%)	94.6% (% early)-onset PET=91%) (late-onset PET=96.2%)
Calxito AC *et al.*[12]	2016	6.14%	84.2%	73.6%	--	
Rezavand N *et al.*[6]	2017	5.07% (mild preeclampsia): 4.33% (severe preeclampsia)	70%	76.7%	85.7%	56%
Present study	2018	9.5%	65.3%	89.3%	94%	50%

H/O: history, C/O : complaint of, PET: Preeclampsia

high-risk conditions are associated with preexisting endothelial dysfunction, which leads to lesser vasodilation of blood vessels in response to reactive hyperemia so they have lesser FMD% cutoff values.

The dysfunction at the endothelial level has been found to be an etiological factor for the development of preeclampsia, such as Cockell *et al.*,[14] who found that in preeclamptic patients FMD was impaired in the subcutaneous artery, thus suggesting the existence of endothelial dysfunction in preeclampsia. Yoshida A *et al.*[15] also reported that FMD decreased in patients with preeclampsia. Retrieving the fact that endothelial dysfunction is a causative factor in the development of the pathogenesis of preeclampsia, FMD can be used as a screening tool for the prediction of the preeclampsia before the presence of clinical signs of the disease.

Acknowledgement

The author sincerely acknowledges and thanks patients for their participation in the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Brandao AH, Felix LR, do Carmo Patricio E, Leite HV, Cabral AC. Difference of endothelial function during pregnancies as a method to predict preeclampsia. Arch Gynecol Obstet 2014;290:471-7.
2. Weissgerber TL. Flow-mediated dilation: Can new approaches provide greater mechanistic insight into vascular dysfunction in preeclampsia and other diseases? Curr Hypertens Rep 2014;16:487.
3. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: A meta-analysis. Int J Cardiovasc Imaging 2010;26:631-40.
4. Brandão AHF, Pereira LMG, Gonçalves ACdeO, Reis ZSN, Leite HV, Cabral ACV. Comparative study of endothelial function and uterine artery Doppler velocimetry between pregnant women with or without preeclampsia development. J Pregnancy 2012:2012:1-5. doi: 10.1155/2012/909315.
5. Bansal N, Verma A, Chandrabhan M, Gupta D, Sharma B, Chakraborty A, *et al.* Impaired flow mediated dilatation – a marker of endothelial dysfunction in preeclampsia. Sch J App Med Sci 2016;4:1180-2.
6. Rezavand N, Veisi F, Zangeneh M, Naghibi SS, Seyedzadeh SMS, Rezaei M. Endothelial function and flow-mediated dilation of brachial artery in pre-eclampsia: Color Doppler ultrasound study. Middle East J Family Med 2017;15:56-62.
7. Kuscu NK, Kurhan Z, Yildirim Y, Tavli T, Koyuncu F. Detection of endothelial dysfunction in preeclamptic patients by using color Doppler sonography. Arch Gynecol Obstet 2003;268:113-6.
8. Mori T, Watanabe K, Iwasaki A, Kimura C, Matsushita H, Shinohara K, *et al.* Differences in vascular reactivity between pregnant women with chronic hypertension and preeclampsia. Hypertens Res 2014;37:145-50.
9. Hamad RR, Eriksson MJ, Silveira A, Hamsten A, Bremme K. Decreased flow-mediated dilation is present 1 year after a pre-eclamptic pregnancy. J Hypertens 2007;25:2301-7.
10. Goynumer G, Yucel N, Adali E, Tan T, Baskent E, Karadag C. Vascular risk in women with a history of severe preeclampsia. J Clin Ultrasound 2012;41:145-50.
11. Kamat R, Jain V, Bahl A. Serial estimation of flow mediated dilatation in women at risk of hypertensive disorders of pregnancy. Int J Cardiol 2011;149:17-22.
12. Calixto AC, Brandão AHF, Toledo LL, Leite HV, Cabral ACV. Prediction of preeclampsia by means of Doppler flowmetry of uterine artery and flow-mediated dilation of brachial artery. Radiol Bras 2014;47:14-7.
13. Oliveira OP, Araujo Júnior E, Lima JW, Salustiano EM, Ruano R, Martins WP, *et al.* Flow-mediated dilation of brachial artery and endothelial dysfunction in pregnant women with preeclampsia: A case control study. Minerva Ginecol 2015;67:307-13.
14. Cockell AP, Poston L. Flow mediated vasodilation is enhanced in normal pregnancy but reduced in preeclampsia. Hypertension 1997;30:247-51.
15. Yoshida A, Nakao S, Kobayashi M, Kobayashi H. Noninvasive assessment of flow-mediated vasodilation with 30-MHz transducer in pregnant women. Hypertension 1998;31:1200-1.