Endothelial function and flow-mediated dilation of brachial artery in pre-eclampsia: color Doppler ultrasound study

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Abstract

Background: Endothelial dysfunction plays an important role in pre-eclampsia pathogenesis. This can be assessed non-invasively by measuring arterial flow-mediated dilation (FMD).

Objective: To compare FMD of the brachial artery and endothelial function between healthy mothers and those who were diagnosed with pre-eclampsia.

Methods: Three groups of pregnant women 20 to 35 years old in gestational weeks 32 to 40 were recruited including healthy subjects (60 cases), mild pre-eclampsia (60 cases), and severe pre-eclampsia (60 cases). FMD of the brachial artery was measured by color Doppler ultrasound and compared between the groups.

Results: Mean FMD values were 9.72%, 5.07%,and 4.33% respectively in the healthy group, mild pre-eclampsia, and severe pre-eclampsia (P< 0.001). According to logistic regression analysis, FMD (adjusted R2 = 25%), RI (adjusted R2 = 17.5%), PI (adjusted R2 = 29.3%), intima-media thickness (adjusted R2 = 43.3%) (P< 0.001) and BMI value (adjusted R2 = 10.3%, P= 0.006) were found to be significant predictors of pre-eclampsia. However, maternal age (adjusted R2 = 1.4%, P= 0.39), gestational age (adjusted R2 = 0.1%, P= 0.98), and parity (adjusted R2 = 5.5%, P= 0.83) were not found as significant predictors of pre-eclampsia. With increasing value of FMD of the brachial artery the likelihood of pre-eclampsia decreased. With increasing value of intima-media thickness, PI, and RI, the likelihood of pre-eclampsia increased. Brachial artery FMD had sensitivity, specificity, PPV, and NPV values of respectively 70%, 76.7%, 85.7%, and 56.1% to predict pre-eclampsia.

Conclusion: Color Doppler ultrasound parameters especially FMD of the brachial artery is a useful non-diagnostic method to predict pre-eclampsia in the third trimester.

Key words: Pregnancy; pre-eclampsia; Doppler ultrasound; endothelium; flow-mediated dilatation

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Introduction

Pre-eclampsia is a multi-organ and serious disease affecting pregnant women after gestational week 20, characterized by new-onset hypertension and proteinuria. It usually presents in the third trimester (1). It is a complicated condition reported as the main cause of morbidity and mortality for both the mother and her fetus. Its incidence is estimated as 3 to 7% of all pregnancies (2). The pathogenesis of pre-eclampsia is multi-factorial and includes maternal, fetal, and placental factors. At the moment, there is no way to prevent this disorder and studies are done to identify those who may be at risk for this pregnancy-specific condition.

One of the pathogenic factors involved in pre-eclampsia is maternal systemic vascular dysfunction which is believed to be due to different factors such as secretion of angiogenic factors that bind to placental and endothelial growth factors. Decreased level of serum placental growth factor in pre-eclamptic women has been shown previously (3). This vascular dysfunction is determined as the main cause of hypertension in pre-eclampsia (4). Endothelial damage is considered as a main factor in pathophysiology of pre-eclampsia (5) and decreased nitric oxide production and endothelium dependent arterial dilation have been shown (6). In addition, production of vasopressor substances can cause vascular endothelial damage as well as vasoconstriction. Hence, several organs including kidneys (proteinuria), brain, and liver may be involved (7-9). Nitric oxide has a critical role in the trophoblast invasion and its availability is required for normal endothelial function (10).

Earlier detection of pre-eclampsia is an important issue and efforts are ongoing to find appropriate diagnostic methods to predict the occurrence of this condition. It is possible to monitor more frequently those who are defined as high risk for developing pre-eclampsia at earlier stages in order to prevent morbidity and mortality. Currently, no agreed upon method exists to predict pre-eclampsia accurately. However, it does not mean that none of the studied variables so far has been useless. Flow-mediated dilation (FMD) is one of the diagnostic methods to study vascular endothelial function, mainly in the brachial artery (11, 12). This method has been studied in first and third trimesters. However, the results show controversy regarding whether this method can be used in conjunction with other clinical and laboratory variables to predict pre-eclampsia (5, 12-14). For instance, FMD in the first trimester was not found to be a valuable predictor factor for pre-eclampsia (13). Another study using FMD in the second trimester also did not demonstrate the predictive effect of this method (7). In contrast, another study showed that changes in FMD values in the second trimester were able to predict pre-eclampsia whether early or late form (12).

A major reason that attracts investigators studying FMD is that it can assess endothelial dysfunction, a major component to the pathophysiology of pre-eclampsia, non-invasively by ultrasound. By this method brachial, radial, or femoral artery diameter changes during pregnancy can be determined (15). Here, we decided to compare FMD of the brachial artery and endothelial function between healthy mothers and those who were diagnosed with pre-eclampsia.

Materials and Methods

Study design

This was a cross-sectional study that lasted for 20 months from 2015 to 2017 in our university hospital obstetrics and radiology departments. Three groups were recruited including healthy mothers, and those with mild pre-eclampsia, and severe pre-eclampsia. Mild pre-eclampsia was defined as systolic blood pressure (BP) of 140 to 160 mmHg, diastolic BP of 90 to 100 mmHg, proteinuria of more than 300 mg/24 h and/or > +2 on two urine samples obtained at least 6 hours apart from each other. Severe pre-eclampsia was defined as systolic BP > 160 mmHg, diastolic BP > 100 mmHg, proteinuria of more than 2 g/24 h and/or > +3 on two urine samples obtained at least 6 hours apart from each other, and presence of any of the following: headache, blurred vision, epigastric pain, elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT), elevated bilirubin, elevated serum creatinine, hemolysis, oliguria (< 30 cc urine per hour), pulmonary edema, or restricted intrauterine fetal growth.

Study population

The study population consisted of women with single pregnancy in gestational weeks 32 to 40 who presented to our obstetrics unit for pregnancy care. Inclusion criteria were age range of 20 to 35 years and single pregnancy. Those with underlying systemic diseases such as cardiovascular, renal, hepatic, and thyroid disorders were excluded.

Study sample

A total number of 180 patients were enrolled into the study in three groups: healthy mothers without pre-eclampsia (60 subjects), mild pre-eclampsia (60 patients), and severe pre-eclampsia (60 patients). The study sample was calculated considering FMD values of 6, 10, and 13.6 (16) respectively in healthy, mild, and severe pre-eclampsia groups. Considering power of 80% and alpha= 5%, the sample size was estimated as at least 60 subjects in each group.

Variables

The studied variables included systolic and diastolic BP, maternal age, gestational week, maternal weight, parity, body mass index (BMI), proteinuria, and ultrasound examination. FMD was measured by color Doppler ultrasound examination of the brachial artery (Samsung Medison, Accuvix® A30). In addition, brachial artery diameter, intima-media thickness, pulsatility index (PI), and resistance index (RI) were documented. The ultrasound examination was done by a board-certified radiologist.

In order to measure BP, sphygmomanometer with appropriate cuff size (cuff length of 80%) was placed on the left arm while the patient was in seated position without

any physical activity for at least the last 10 minutes. For those who were not able to sit still, BP of the left arm was measured while the patient was lying on her left side. Laboratory tests including urine protein and analysis, hepatic transaminases, renal function tests were also recorded. All the variables documented were entered into a pre-designed checklist of data collection. The data were gathered by an obstetrics resident and supervised by a board certified obstetrician. The final diagnosis of mild and severe pre-eclampsia was made by the obstetrician.

Statistical analyses

Descriptive indices including frequency, percentage, mean and its standard deviation (SD) were used to express data. The normal distribution of continuous data was determined using the Kolmogorov-Smirnov test. In order to compare categorical variables between the studies groups, the chi-squared test was used. In comparison of continuous data among the three groups, normally distributed data were compared by analysis of variance (ANOVA) and Kruskal-Wallis test was applied for those with non-normal distribution. In comparison of continuous data between the two groups (healthy vs. pre-eclampsia), the Student's t test or Mann-Whitney U test was used. A logistic regression model was developed to determine the significant risk factors for pre-eclampsia. A p value of less than 5% was considered statistically significant. In addition, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) values of the variables were calculated using cross-tabulations and yielded true positive (sensitivity) and true negative (specificity) statistics.

Ethics

The study protocol was verified by the Research Council Ethics Committee of our medical university. The study objectives were explained to the patients and they were asked to provide written consent for enrolment. The study was in conformity with the Declaration of Helsinki.

Results

Table 1 shows comparison of maternal age, gestational age, BMI, and systolic and diastolic BP values among the three studied groups. As observed, except for maternal age which did not show difference among the groups, other variables showed significant difference between the groups.

Table 1: Comparison of age, gestational age, parity, body mass index among three groups of pregnant women: healthy subjects, mild-preeclampsia, and severe pre-eclampsia

	Healthy group (N= 60)	Mild pre-eclampsia (N= 60)	Severe pre-eclampsia (N= 60)	P value
Maternal age, year	29.98 (±4.08)	30.15 (±3.24)	30.02 (±3.92)	0.96[a]
Gestational age, week	34.7 (±2.06)	35.42 (±2.04)	34.28 (±1.9)	0.008[a]
BMI, kg/m²	25.16 (3.77)	28.5 (4.7)	27.82 (5.03)	< 0.001[a]
Systolic BP	110.08 (13.88)	137.27 (7.05)	164.78 (11.34)	< 0.001[a]
Diastolic BP	69.17 (0.87)	83.42 (0.76)	99.5 (1.03)	< 0.001[a]

Abbreviations: BMI= body mass index, BP= blood pressure. Data are presented as mean (±standard deviation); [a] ANOVA (analysis of variance)

Table 2 shows frequency distribution of subjects in the categories of the variables. About 51.7% of patients in the severe pre-eclampsia group were older than 30 years. About 53.3% of patients with severe pre-eclampsia were within the gestational age of 32 to 34 weeks. As seen in Table 2, 23.3% of severe pre-eclamptic women had BMI values of 32 to 39 kg/m2. As observed, 40% of patients in the severe pre-eclampsia group experienced pre-eclampsia in their first pregnancy.

Table 3 presents frequency distribution of patients in each group according to systolic and diastolic BP values as well as proteinuria grade. A higher percentage of patients in the severe pre-eclampsia group had +3 proteinuria. There was significant difference (P < 0.001) among the three groups regarding proteinuria grade.

Table 4 shows comparison of color Doppler ultrasound examination findings among the three studied groups. Mean FMD values were 9.72%, 5.07% and 4.33% respectively in the healthy group, and the mild pre-eclampsia, and severe pre-eclampsia groups (P< 0.001). About half of the patients with severe pre-eclampsia had intima-media thickness of 0.5 to 0.65 mm.

Table 2: Frequency distribution of subjects in the categories of the variables among three groups of pregnant women: healthy subjects, mild-preeclampsia, and severe pre-eclampsia

		Healthy group (N= 60)	Mild pre-eclampsia (N= 60)	Severe pre-eclampsia (N= 60)
Age, year	20-25	10 (16.7%)	1 (1.7%)	11 (18.3%)
	25-30	21 (35%)	32 (53.3%)	18 (30%)
	30-35	29 (48.3%)	27 (45%)	31 (51.7%)
Gestational age, week	32-34	28 (46.7%)	21 (35%)	32 (53.3%)
	34-36	19 (31.7%)	18 (30%)	20 (33.3%)
	36-38	12 (20%)	19 (31.7%)	8 (13.3%)
	38-40	1 (1.7%)	2 (3.3%)	0
BMI, kg/m²	18-25	31 (51.7%)	15 (25%)	24 (40%)
	25-32	26 (43.3%)	30 (50%)	22 (36.7%)
	32-39	3 (5%)	15 (25%)	14 (23.3%)
Parity	1	23 (38.3%)	26 (43.3%)	24 (40%)
	2	20 (33.3%)	16 (26.7%)	14 (23.3%)
	3	10 (16.7%)	15 (25%)	20 (33.3%)
	4	4 (6.7%)	1 (1.7%)	1 (1.7%)
	5	3 (5%)	2 (3.3%)	1 (1.7%)

Table 3. Frequency distribution of patients in each group according to systolic and diastolic BP values and proteinuria grade

		Healthy group (N= 60)	Mild pre-eclampsia (N= 60)	Severe pre-eclampsia (N= 60)
Systolic BP, mmHg	90 to 130	59 (98.3%)	14 (23.3%)	1 (1.7%)
	130 to 180	1 (1.7%)	46 (76.7%)	59 (98.3%)
Diastolic BP, mmHg	60 to 85	59 (98.3%)	38 (63.3%)	4 (6.7%)
	85 to 120	1 (1.7%)	22 (36.7%)	56 (93.3%)
Proteinuria	0	35 (58.3%)	15 (25%)	0
	+1	24 (40%)	34 (56.7%)	1 (1.7%)
	+2	1 (1.7%)	11 (18.3%)	7 (11.7%)
	+3	0	0	52 (86.7%)

Table 4. Comparison of color Doppler ultrasound examination findings among the three studied groups

	Healthy group (N= 60)	Mild pre-eclampsia (N= 60)	Severe pre-eclampsia (N= 60)	P value
Intima-media thickness, mm	0.3 (±0.05)	0.37 (±0.04)	0.49 (±0.08)	< 0.001[a]
Pulsatility index, cm/sec	2.26 (±0.39)	3.19 (±0.85)	3.9 (±0.78)	< 0.001[b]
Resistance index, cm/sec	0.81 (±0.07)	0.85 (±0.06)	0.88 (±0.05)	< 0.001[b]
FMD, %	9.72 (±4.87)	5.07 (±3.03)	4.33 (±2.28)	< 0.001[b]

Data are presented as mean (±standard deviation); [a] ANOVA (analysis of variance); b Kruskal-Wallis

Table 5 (next page) shows frequency distribution of subjects in the categories of the color Doppler ultrasound findings among the three groups of pregnant women. As observed, 60% of patients in the severe pre-eclampsia group had PI values of 3.9 to 6.2 cm/sec.

Table 5: Frequency distribution of subjects in the categories of the color Doppler ultrasound findings among three groups of pregnant women

		Healthy group (N= 60)	Mild pre-eclampsia (N= 60)	Severe pre-eclampsia (N= 60)
Intima-media thickness, mm	0.2 to 0.35	49 (81.7%)	24 (40%)	3 (5%)
	0.35 to 0.5	11 (18.3%)	36 (60%)	29 (48.3%)
	0.5 to 0.65	0	0	28 (46.7%)
PI, cm/sec	1.6 to 3.9	59 (98.3%)	45 (75%)	24 (40%)
	3.9 to 6.2	1 (1.7%)	15 (25%)	36 (60%)
RI, cm/sec	0.82 to 0.64	41 (68.3%)	24 (40%)	12 (20%)
	0.82 to 1	19 (31.7%)	36 (60%)	48 (80%)
FMD, %	0 to 12	45 (75%)	60 (100%)	60 (100%)
	12 to 24	15 (25%)	0	0

Abbreviation: PI= pulsatility index, RI= resistance index, FMD= flow-mediated dilation

According to logistic regression analysis, FMD (adjusted R2 = 25%), RI (adjusted R2 = 17.5%), PI (adjusted R2 = 29.3%), intima-media thickness (adjusted R2 = 43.3%) (P< 0.001) and BMI value (adjusted R2 = 10.3%, P= 0.006) were found to be significant predictors of pre-eclampsia. However, maternal age (adjusted R2 = 1.4%, P= 0.39), gestational age (adjusted R2 = 0.1%, P= 0.98), and parity (adjusted R2 = 5.5%, P= 0.83) were not found as significant predictors of pre-eclampsia. With increasing value of FMD of the brachial artery the likelihood of pre-eclampsia decreased. With increasing value of intima-media thickness, PI, and RI, the likelihood of pre-eclampsia increased.

Brachial artery FMD had sensitivity, specificity, PPV, and NPV values of respectively 70%, 76.7%, 85.7%, and 56.1% to predict pre-eclampsia.

Discussion

According to the obtained findings, color Doppler ultrasound parameters especially FMD of the brachial artery is a useful method to predict pre-eclampsia in the third trimester. Prediction of pre-eclampsia is a critical issue in obstetrics as pre-eclampsia, despite improvements in its diagnosis and management, has significant morbidity and mortality. Some clinical characteristics have been proposed as potential risk factor for pre-eclampsia such as nulliparity, older maternal age, higher BMI values, previous history of pre-eclampsia, etc (17). However, no definite factor can accurately predict pre-eclampsia and this condition still remains one of the challenging diagnoses for obstetricians for which the only treatment is delivery. Our findings showed that higher BMI values were associated with pre-eclampsia which is compatible with previous reports. However, regression analysis did not show parity, gestational age, or maternal age to be significant predictive values for pre-eclampsia. Since patients at higher risk of pre-eclampsia need more meticulous attention to assure a safe pregnancy and avoid complications such as intrauterine growth retardation (IUGR), recognizing women who are susceptible to this condition has always been a fascinating research topic for investigators.

One of the fascinating diagnostic methods that has gained attention in recent years is studying endothelial function. This can be assessed by several methods such as serum markers (Endothelin-1, nitric oxide, vascular cell adhesion molecules, etc (14). Another method is determining the dilation of the artery by Doppler ultrasound (5, 6, 18, 19). Most studies have shown reduced FMD in pre-eclampsia in comparison to normotensive subjects (5, 12). Although FMD has been studied in several arteries including uterine and ophthalmic arteries (20), the brachial artery is the most widely studied artery in this setting.

Our study findings are in agreement with these results that brachial artery FMD was significantly lower in the pre-eclampsia group compared to the healthy group. Here, we included patients who were diagnosed with pre-eclampsia considering the established clinical and laboratory variables. The usefulness of FMD has also been in patients who were presumed to develop pre-eclampsia. For example, a previous study showed that endothelial function impairment occurs long before the development of pre-eclampsia, even as soon as the first trimester (21). Furthermore, patients with previous history of pre-eclampsia had lower FMD and decreased arterial dispensability compared to those without previous history of pre-eclampsia (22).

Although several studies have addressed the utility of FMD in pre-eclampsia, there is controversy in the literature regarding FMD changes in prediction of pre-eclampsia. Some studies showed results which are in agreement with ours (5, 23-25). However, some studies challenge the utility of this method to predict pre-eclampsia. For example, in a study (13) including 487 pregnant women in the first trimester, brachial artery FMD in the unaffected group (7.4%) was not considerably different (P= 0.37) from late-onset pre-eclampsia (5.6%) and early-onset pre-eclampsia (11.4%). The authors concluded that FMD in the first trimester did not predict the occurrence of pre-eclampsia.

Another recent study including 14 healthy pregnant women and 14 patients with pre-eclampsia showed that FMD was significantly lower in the pre-eclampsia group (4.83%) vs. healthy group (8.53%) (26).

When evaluating the obtained findings and the available evidence, although some conflicting results exist, it seems that brachial artery FMD can be used as a non-invasive method to diagnose pre-eclampsia. However, it should be mentioned that a gold standard test for determining endothelial function is still unavailable and we think that future studies include other markers of endothelial dysfunction in pre-eclampsia with longer follow-ups to elucidate the role of FMD by brachial artery ultrasound examination more accurately.

Limitations

We faced some limitations in this study. We were not able to follow the pregnancies to find out the outcomes regarding delivery and neonatal factors. Even, some studies have proposed that mothers with pre-eclampsia are more susceptible to cardiovascular diseases later in their life (2). We think that longer follow-ups can elucidate more dimensions of this condition.

Conclusion

Due to changes in vascular function during pre-eclampsia, Doppler ultrasound examination of the brachial artery showed that the obtained parameters including intima-media thickness, PI, RI, and FMD were significant predictors for pre-eclampsia. As this method is non-invasive and can be done quickly at the bedside, we recommend that clinicians use this method to diagnose pre-eclampsia.

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