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Evaluation of Maternal Ophthalmic Artery Doppler Velocimetry at 18 to 24 Weeks of Gestational Age in the Prediction of Preeclampsia

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Abstract

Background Preeclampsia (PE) is a crucial health issue that complicates roughly 10% of gestations and causes more than 50,000 deaths yearly worldwide. Most women with PE have mildly high blood pressure, a small amount of excess protein in the urine, and they do not experience any symptoms of the disease. This is the reason that prenatal screening of increased blood pressure is done in later pregnancy period.

Aims and Objectives The aim of this study was to evaluate the role of maternal ophthalmic artery Doppler velocimetry in predicting PE. The objectives were to examine the velocimetry values in the women undergoing antenatal scan at 18 to 24 weeks of gestation and their potential value in the subsequent development of PE.

Materials and Methods A prospective observational study was conducted on 800 women who visited the hospital for antenatal ultrasound at 18 to 24 gestational weeks. Ophthalmic artery Doppler study was conducted to obtain the spectral waveform from both eyes after recording the patient history. Doppler indices like first peak systolic velocity (PSV1), second peak systolic velocity (PSV2), pulsatility index (PI), end-diastolic velocity (EDV), resistivity index (RI), systolic/diastolic ratio (S/D), and PSV2 to PSV1 ratio (PSV ratio: PSV2/PSV1) were obtained and their average values were obtained. All patients were then followed up till termination of pregnancy to document the development of PE.

Statistical Analysis The collected data were entered into the Microsoft Excel and then analyzed and statistically evaluated using SPSS-25 version.

Results The study revealed that a total 95 subjects developed PE (11.9%) from a total of 800 subjects. The ophthalmic artery PSV2/PSV1 ratio and PSV2 of right and left eye were significantly increased in patients with PE. The EDV in pre-eclamptic patients was also increased as compared to normotensive patients. The average values of the PI and

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- Doppler
- ophthalmic artery
- peak systolic velocity ratio
- pre-eclampsia
- velocimetry

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RI were decreased in PE patients as compared to normotensive patients. The S/D ratio was also decreased in patients who later developed PE as compared to normotensive patients.

Conclusion Ophthalmic artery Doppler velocimetry can detect PE in early stages and is a cheap, noninvasive, readily available, safe, and reliable tool for evaluation of hemodynamic changes in normotensive pregnancy, and even more so in PE. The most reliable parameters being the PSV2 and PSV2/PSV1 ratio with sensitivity of both the parameters being more than 90%. The other parameters like increased EDV and decreased PI and RI also have some role.

Introduction

Pre-eclampsia (PE) is a hypertensive disorder related to pregnancy, induced usually at around 20 weeks of gestational age. It is a multi-systemic hypercoagulable disorder characterized by increased vascular resistance of systemic vasculature induced by abnormal placental vascular response and endothelial dysfunction.[1,2] It is a common cause of morbidity and mortality with a global incidence of 5 to 10%.[3] It presents with complications in the eyes in 30 to 100% of patients.[4] About 25% of women who suffer from severe PE are affected by visual disturbances, but blindness is rare. The ophthalmic artery (OA) is the first internal carotid artery branch and is anatomically and embryologically similar to the intracranial vasculature and is an easily approachable artery for ultrasonographic Doppler assessment. This artery functionally simulates the hemodynamics of the less approachable intracranial circulation. Moreover, Doppler study is a safe and accessible method and can be done in the least time. OA Doppler (OAD) velocimetry in the previous studies suggests that impedance to flow decreases and velocities increase in pregnancies with PE in comparison to normotensive pregnancies.[5,6]

As PE cannot be prevented, the management is solely based on an identification of high-risk women, and close clinical and laboratory monitoring to diagnose the disease in its early stages. New parameters need to be identified to determine severe cases of PE to start a more intensive treatment for pregnant women.

Materials and Methods

The study comprises of 800 women who visited for antenatal ultrasound at 18 to 24 weeks of gestation at the Department of Radiodiagnosis and Imaging, Sri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Amritsar. The maternal demographic data and relevant clinical history of the participants were recorded after clearance from the Ethics Committee. Informed consent was obtained from all the participants of the study.

The study was performed with a GE Voluson E8 using a linear 5–10 MHz transducer. The patient was placed in the supine position at rest for 5 minutes. After closing the eyelid and applying the contact gel, the transducer probe was placed gently over the patient's eyelid. Color Doppler mode was used for the identification of the OA. It is situated supero-medial to the hypoechoic structure, that is the optic nerve. (►**Fig. 1**) Then the pulsed-wave Doppler mode was used for recording the waveforms from each eye alternatively (i.e., first right eye then left eye followed by right eye and then left eye again; ►**Figs. 2** and **3**). Sample gate of 2 mm and an insonation angle of $<20°$ were used.[7] At least five consecutive waves were recorded.[8] To minimize any potential adverse effects on the eyes, the duration of the examination was a few seconds, and a special preset was used with a marked reduction in output power and a maximum mechanical index of 0.4. The Doppler indices recorded were the first and second peak systolic velocity (PSV1, PSV2), the ratio of PSV2 to PSV1 (PSV2/PSV1), end-diastolic velocity (EDV), pulsatility index (PI), resistivity index (RI) and systolic/diastolic (S/D) ratio. The PSV1 and PSV2 were manually measured from the waveform, and then the PSV ratio was calculated.[7] The rest of the parameters were measured by the machine automatically. The average of the two values from each eye was calculated.[9]

The patient was then followed up for any subsequent development of PE during the pregnancy. The subjects were diagnosed to be pre-eclamptic by the following finding: new onset of hypertension (systolic blood pressure [SBP] of >140 mm Hg or diastolic blood pressure [DBP] of >90 mm Hg on at least two occasions 4 hours apart that developed

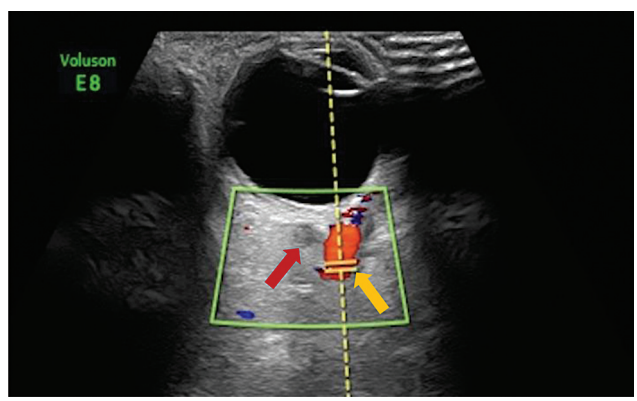

Fig. 1 Image showing spectral and color mode Doppler representing the ophthalmic artery (yellow arrow) medial to the optic nerve (red arrow).

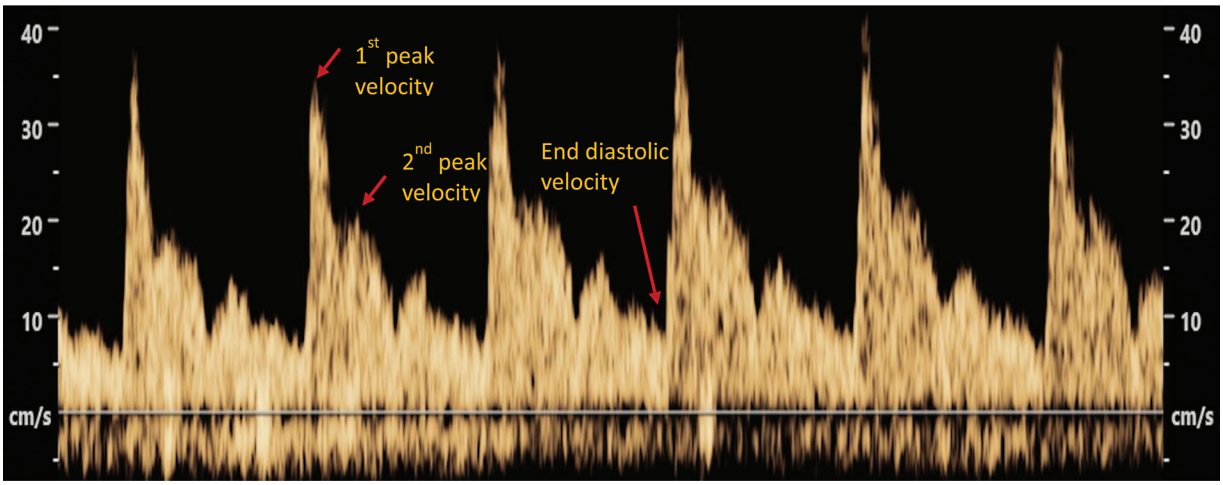

Fig. 2 This image represents the spectral waveform of the ophthalmic artery with the arrows representing the first PSV, second PSV, and the end-diastolic velocity. PSV, peak systolic velocity.

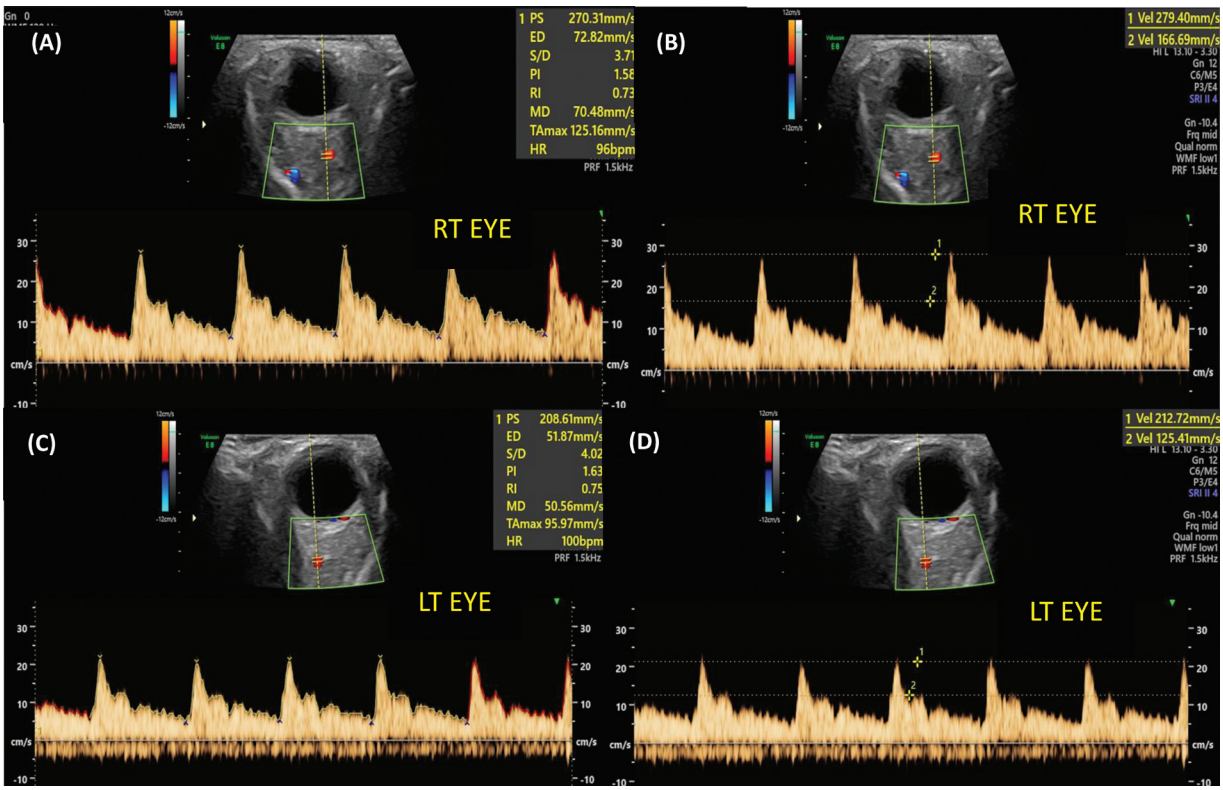

Fig. 3 This spectral Doppler represents the various parameters of the ophthalmic artery velocimetry measured alternatively form both eyes. All the parameters are measured automatically (**A** and **C**) except the first and second peak systolic velocity, which were measured manually (**B** and **D**).

after 20 weeks of gestation in previously nonhypertensive women) or renal dysfunction with serum creatinine levels of >97 µmol/L with no underlying renal disease, hepatic dysfunction with blood transaminase levels of more than two times the upper normal limit (≥65 IU/L), thrombocytopenia with platelet count <100,000/µL, neurological symptoms like visual or cerebral symptoms, or pulmonary edema.[10]

The exclusion criteria for our study were preconceptional hypertensive patients, patients on medications other than routinely used supplementation in pregnancy, patients who were already on treatment for PE, patients with known ophthalmic pathology, and pregnancies with congenital abnormalities in the fetus. Equipment used- Ultrasound machine - Voluson E8 Expert BT12 (Wipro GE)with linear 5–10MHz probe and convex rab 6D (2–7) MHz probe.

Statistical Analysis

The data collected were first entered in Microsoft Excel. They were analyzed and evaluated statistically using SPSS-25 version. Normality of each of the variable was assessed using the Kolmogorov–Smirnov test. Quantitative data were

expressed by calculating the mean and standard deviation, and differences between means of two groups were tested by unpaired *t*-test or Mann–Whitney U-test, while qualitative data were expressed in percentage and differences between percentages of two groups were tested by chi-square test or Fisher exact test. The receiver operating characteristic (ROC) curve was prepared using OA parameters to differentiate between non-PE and PE. Cut-off value was calculated using Youden index, and sensitivity, specificity, positive predictive value, and negative predictive value were calculated to differentiate between non-PE and PE. A *p*-value of less than 0.05 was considered statistically significant.

Results

The study included 800 subjects, out of which 95 pregnancies developed PE on follow-up based on clinical or biochemical findings or both. In this study, the pulsed wave velocimetry parameters that were increased in the patients who later developed PE as compared to the normotensive patients were PSV2, PSV2/PSV1, and EDV. Parameters like PI, RI, and S/D were decreased in the subjects who later developed PE. PSV1 did not correlate with whether the patient later developed PE or not.

The average PSV2 among the subjects who later developed PE was 22.18 ± 4.51 and that among the subjects who did not develop PE was 16.22 ± 3.66 (p-value < 0.001). Similarly, the average PSV ratio among the PE subjects was 0.66 ± 0.10 and that among the non-PE subjects was 0.49 ± 0.07 (p-value < 0.001). The average EDV among the PE subjects and non-PE subjects was 6.37 ± 0.99 and 5.76 ± 1.54, respectively (p-value < 0.001). The average PI, RI, and S/D values among the subjects who later developed PE came out to be 2.15 ± 0.36, 0.80 ± 0.04, 5.34 ± 1.09, respectively. The average PI, RI, and S/D values among the non-PE subjects were 2.43 ± 034, 0.82 ± 0.04, and 6.07 ± 1.85, respectively (p-value < 0.001). The average PSV1 among the PE subjects and non-PE subjects was 33.13 ± 3.73 and 33.05 ± 6.71, respectively (p-value $= 0.87$), which was not significant statistically (►**Table 1**).

Table 1 Comparison of ophthalmic artery parameter between non-PE group and PE group ($n = 800$)

	Non-PE group ($n = 705$)	PE group ($n = 95$)	*p*-Value
PSV1	33.05 ± 6.71	33.13 ± 3.73	**0.87**
PSV2	16.22 ± 3.66	22.18 ± 4.51	<**0.001**
PSV2:PSV1	0.49 ± 0.07	0.66 ± 0.10	<**0.001**
PI	2.43 ± 034	2.15 ± 0.36	<**0.001**
RI	0.82 ± 0.04	0.80 ± 0.04	<**0.001**
S/D	6.07 ± 1.85	5.34 ± 1.09	<**0.001**
EDV	5.76 ± 1.54	6.37 ± 0.99	<**0.001**

Abbreviations: EVD, end-diastolic velocity; PE, pre-eclampsia; PI pulsatility index; PSV1, first peak systolic velocity; PSV2, second peak systolic velocity; RI, resistivity index; S/D, systolic/diastolic.

Table 2 Comparison of BP between non-PE group and PE group ($n = 800$)

	Non-PE group ($n = 705$)	PE group ($n = 95$)	*p*-Value
SBP (mm Hg)	117.87 ± 8.38	149.22 ± 9.29	<**0.001**
DBP (mm Hg)	78.42 ± 5.70	91.79 ± 6.99	<**0.001**
MAP (mm Hg)	91.49 ± 5.75	110.72 ± 7.70	<**0.001**

Abbreviations: DBP, diastolic blood pressure; MAP, mean arterial pressure; PE, pre-eclampsia; SBP, systolic blood pressure.

The number of study subjects with age groups <20 years, between 21 and 30 years, >30 years was 5, 65, and 25, respectively, among the PE subjects and those among the non-PE subjects were 66, 452, and 187, respectively. The PE subjects had a mean age of 28.12 ± 5.01 years and that of non-PE subjects was 28.28 ± 5.63 years (p-value $= 0.78$). The mean body mass index (BMI) among the PE and non-PE subjects was 25.45 ± 2.21 and 25.89 ± 2.71 kg/m^2, respectively, (p-value $= 0.13$). In this study, the age and BMI difference among the PE and non-PE subjects was not significant.

The mean SBP, mean DBP, and the mean arterial pressure (MAP) among the PE subjects were 149.22 ± 9.29, 91.79 ± 6.99, and 110.72 ± 7.70 mmHg, respectively, and among the non-PE subjects were 117.87 ± 8.38, 78.42 ± 5.70, and 91.49 ± 5.75 mmHg, respectively (p-value < 0.001; ►**Table 2**).

In this study, the cut-off value of PSV2 in predicting PE came out to be 19.15 cm/s with a sensitivity of 88.42% and a specificity of 80.85%. Similarly, the cut-off value for PSV ratio was 0.565 cm/s with a sensitivity of 90.53% and a specificity of 83.69%. The cut-off value for EDV was 5.25 cm/s with a sensitivity of 97.37% and a specificity of 43.48% (►**Table 3** and ►**Fig. 4**). The parameters like PI, RI, and S/D were decreased in PE subjects as compared to non-PE subjects (►**Table 4** and ►**Fig. 5**).

Discussion

PE is a condition that leads to maternal morbidity and mortalities worldwide; so early diagnosis of PE is very crucial to identify the high-risk pregnancies for timely and intensive management to prevent fetal and maternal complications of PE. Therefore, for early prediction of PE, some markers are necessary. Hemodynamic changes in the maternal cardiovascular system precede the clinical signs of PE, which are apparent in the first trimester. These include an increase in peripheral vascular resistance and cardiac output.[11,12] Therefore, PE is preceded by cerebral circulation alterations.

The OA being the first internal carotid artery branch simulates the intracranial vessels functionally, anatomically, and embryologically. The OA branches supply the orbit, upper nose, face, and meninges.[13] OA having easy access for ultrasonographic examination gives useful information about intracranial circulation, which is not easy to access. Doppler sonography of OA is done trans-orbitally and is a noninvasive approach for indirectly detecting hemodynamic changes in intracranial circulation in pregnancy.

Table 3 Diagnostic value using ophthalmic artery parameter to differentiate between non-PE group and PE group

	PSV2		PSV2:PSV1		EDV	
	Value	95% CI	Value	95% CI	Value	95% CI
Cut-off value	19.15		0.565		5.25	
Sensitivity	88.42%	83.00–92.60%	90.53%	85.44–94.29%	97.37%	93.97–99.14%
Specificity	80.85%	78.70–82.87%	83.69%	81.65–85.58%	43.48%	40.87–46.11%
Positive likelihood ratio	4.62	4.10–5.20	5.55	4.89–6.30	1.72	1.64–1.81
Negative likelihood ratio	0.14	0.10–0.21	0.11	0.07–0.18	0.06	0.03–0.14
Positive predictive value	38.36%	35.59–41.20%	42.79%	39.71–45.92%	18.84%	18.07–19.64%
Negative predictive value	98.11%	97.22–98.72%	98.50%	97.69–99.03%	99.19%	98.10–99.66%
Accuracy	81.75%	79.77–83.61%	84.50%	82.63–86.24%	49.88%	47.40–52.35%

Abbreviations: CI, confidence interval; EVD, end-diastolic velocity; PE, pre-eclampsia; PSV1, first peak systolic velocity; PSV2, second peak systolic velocity.

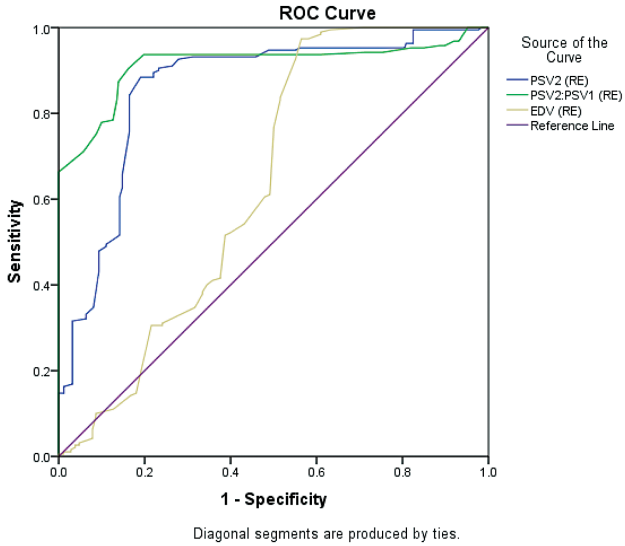

Fig. 4 ROC curve analysis using ophthalmic artery parameter to differentiate between non-PE group and PE group. PE, pre-eclampsia; ROC, receiver operating characteristic.

Our study of maternal OAD velocimetry on pregnancies at 18 to 24 weeks of gestation revealed that the Doppler parameters are potential markers for early prediction of PE development. The Doppler indices recorded in our study were the PSV1 and PSV2, the ratio of PSV2 to PSV1, EDV, PI, RI, and S/D. Out of these indices, the values of second peak velocity, ratio of two systolic peaks velocities (PSV2/PSV1), and EDV were found to be increased significantly in the subjects who later developed PE as compared to the ones who did not develop PE. The PI, RI and S/D were decreased in the PE subjects than non-PE subjects. The first peak velocity was not found to be statistically significant for PE development.

The PSV2 and PSV ratio had statistically significant sensitivity and specificity in predicting PE at 18 to 24 gestational weeks, while EDV had good sensitivity but poor specificity. Other values like PI, RI, and S/D ratios were decreased in the subjects who later developed PE. A previous study on maternal OAD at 19 to 23 gestational weeks that recorded PSV1, PSV2, PI, and the ratio of PSV2 to PSV1 concluded that PSV2 and PSV ratio were raised whereas PI was not altered in the subjects who developed PE.[7]

Another study was conducted on maternal OAD with 148 patients at 35 to 37 weeks of gestation, out of which 48 were known preeclamptic and 100 were non-preeclamptic and PSV1, PSV2, ratio of PSV2 to PSV1, and PI were calculated from both eyes.[9] Their average values were calculated. The average PSV2 and average value of PSV ratio of both eyes were higher in PE patients as compared to non-PE patients. The average PI from both eyes along with their average values

Table 4 Diagnostic value using ophthalmic artery parameter to differentiate between non-PE group and PE group

	PI		RI		S/D ratio	
	Value	95% CI	Value	95% CI	Value	95% CI
Cut-off value	2.01		0.845		7.06	
Sensitivity	52.63%	45.28–59.90%	82.11%	75.90–87.28%	100.00%	98.08–100.00%
Specificity	88.65%	86.88–90.26%	34.18%	31.71–36.73%	77.52%	75.25–79.67%
Positive likelihood ratio	4.64	3.80–5.66	1.25	1.16–1.35	4.45	4.04–4.90
Negative likelihood ratio	0.53	0.46–0.62	0.52	0.38–0.72	0.00	
Positive predictive value	38.46%	33.88–43.26%	14.39%	13.48–15.36%	37.48%	35.23–39.77%
Negative predictive value	93.28%	92.27–94.17%	93.41%	91.20–95.10%	100.00%	99.66–100.00%
Accuracy	84.37%	82.50–86.12%	39.87%	37.46–42.32%	80.19%	78.15–82.12%

Abbreviations: CI, confidence interval; PE, pre-eclampsia; PI pulsatility index; RI, resistivity index; S/D, systolic/diastolic.

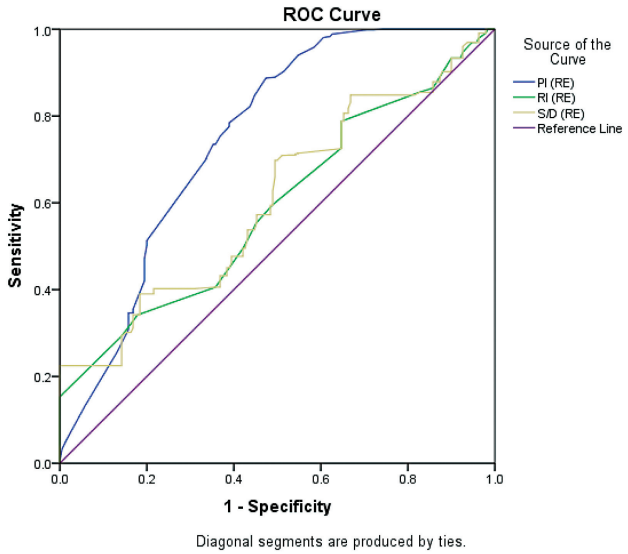

Fig. 5 ROC curve analysis using ophthalmic artery parameter to differentiate between non-PE group and PE group. PE, pre-eclampsia; ROC, receiver operating characteristic.

were decreased in PE patients in comparison to non-PE patients. These findings are similar to our study, but, in our study, the RI and S/D were also reduced in PE subjects. EDV is the additional parameter, which was raised in PE patients. Our study had a much higher sample size (total 800) and had a prospective design in which OAD was done first at an earlier stage of gestation, that is 18 to 24 weeks on random subjects rather than prior knowledge of preeclamptic status. The sample size was higher in our study, which increases the detection value, and early detection aids in the early and intensive management of this condition. A study with a sample size of 120 patients had increased OA parameters like PSV1, PSV2, peak ratio, and EDV in the group that had PE as compared to the non-PE group, and RI and PI were decreased in the PE group as compared the non-PE group.[7] Our study had no relation between PSV1 and the development of PE, but our study had a higher sample size. In a few of the previous studies, high-risk patients were part of the study and Doppler was done only on the right eye.[14,15] In one of such studies conducted at 18 to 23 gestational weeks, no significant difference was detected concerning PSV2, PSV ratio, or PI between the PE and non-PE groups.[15]

A meta-analysis was conducted in accordance with PRISMA guidelines to evaluate the accuracy OAD parameters in the diagnosis of PE.[16] The parameters included were peak systolic velocity, EDV, second systolic velocity peak, resistance index, PI, and peak ratio between PE cases and controls, similar to our study. Eight studies stratified 1,425 pregnant women into mild and severe or late and early PE. In their study, peak ratio and second systolic velocity peak had better diagnostic performance than the other indexes, with the peak ratio of Area under the receiver operating characteristic curve (AUCROC) at 0.885, with the sensitivity of 84% and a specificity of 92%, and a low false-positive rate of 0.08. The second systolic velocity peak had AUCROC of 0.926, with the sensitivity of 85% and specificity of 88%. Similarly in the present study, the ROC curve plot of PSV2/PSV1 had the cut-off value of 0.565 for prediction of development of PE with sensitivity (95% confidence interval [CI]) of 90.53% (85.44–94.29%) and specificity (95% CI) of 83.69% (81.65–85.58%). The AUROC value was 0.914 with 95% CI values of 0.884 to 0.945. The ROC curve plot of PSV2 had the cut-off value of 19.15 cm/s for prediction of development of PE with sensitivity (95% CI) of 88.42% (83.00–92.60%) and specificity (95% CI) of 80.85% (78.70–82.87%). The AUROC value was 0.857 with 95% CI values of 0.830 to 0.885.

Another prospective observational study was conducted on 6,746 women visiting the hospital at 35 to 36 weeks of gestation that used noninvasive devices that were operator-independent to record various hemodynamic parameters like pulse wave velocity, cardiac output, central systolic and diastolic blood pressures, stroke volume, augmentation index, total peripheral resistance, heart rate of the fetus, MAP, uterine artery PI, and serum placental growth factor levels.[17] They concluded that SBP and DBP, peripheral vascular resistance, pulse wave velocity, and augmentation index had higher values in those who developed PE. Another prospective observational study was conducted at $35+0$ to $36+6$ weeks of gestation.[18] Various demographic parameters along with maternal factors and OA second to first peak systolic velocity ratio, MAP, uterine artery PI, serum placental growth factor, and serum sFlt-1 were recorded. They concluded that the PSV ratio had value in the prediction of PE. These two studies though prospective and noninvasive were done in the late pregnancy period while our study has the potential to predict PE in the early stage of gestation.

A prospective cohort study was conducted on 200 women at 19 to 23 weeks of gestation.[19] They were divided into low-risk groups and high-risk groups for PE development. Their results showed that PSV2/PSV1 had higher values in high-risk patients than in low-risk women. The preliminary known high-risk and low-risk women might act as confounding factors, which was not the case in our study.

Conclusion

This study shows that the OA spectral Doppler velocimetry done on mothers at 18 to 24 gestational weeks can detect early in the Doppler parameters of patients who later develop PE. These changes include raised values of PSV2, PSV ratio, EDV, and a decrease in PI, RI, and S/D in pre-eclamptic patients as compared to non-PE subjects. So maternal OAD velocimetry is useful for early prediction of PE, hence aiding in its timely management.

Conflict of Interest
None declared.

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