ORIGINAL ARTICLE

Comparison of ophthalmic artery Doppler velocimetry changes on patients with hypertensive disorders of pregnancy versus normotensive pregnant women in third trimester of pregnancy: A prospective study

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Abstract

Background: Hypertensive disorders in pregnancy are widely acknowledged as among the most severe complications, significantly impacting maternal as well as neonatal morbidity and mortality rates globally. Preeclampsia is the most important gestational condition associated with hypertension. *Aim and Objectives*: To compare Ophthalmic Artery Doppler (OAD) indices of normotensive and hypertensive pregnant women in third trimester of pregnancy and to correlate the OAD changes with the severity of hypertensive disorder of pregnancy in third trimester. *Material and Methods:* A prospective study was conducted in a tertiary care hospital, Mysuru. Seventy pregnant women with hypertensive disorders and 70 normotensive pregnant women were enrolled in this study during their third trimester. A comprehensive history of hypertension was obtained, and an obstetric scan was conducted to assess the gestational age. Doppler examinations of the umbilical, middle cerebral, and uterine arteries were also performed. At the same time, maternal ophthalmic artery Doppler readings were obtained, and the women were monitored after birth. The perinatal outcomes were also documented. *Results:* Statistically significant differences were observed in ophthalmic artery Doppler parameters' mean values between normotensive women and those with hypertensive disorders of pregnancy, particularly for peak systolic velocity, pulsatility index, and resistivity index. *Conclusion:* Pregnancy complicated by hypertensive disorders showed significant differences in ophthalmic artery Doppler velocities between women with preeclampsia and healthy pregnant women. These findings imply that ophthalmic artery Doppler parameters can be considered predictable indicators of the development of preeclampsia. These parameters, which include safety, cost-effectiveness, and accessibility, can be used to distinguish between preeclamptic and normotensive pregnancies during late gestation.

Keywords: Ophthalmic Artery Doppler, Normotensive, Hypertension, Preeclampsia, End Diastolic Velocity, Peak Systolic Velocity

Introduction

Maternal mortality continues to pose a significant challenge on a global scale, as it is estimated that approximately 810 women lose their lives on a daily basis due to complications related to pregnancy or childbirth. Hypertension is the most prevalent disorder affecting pregnancies worldwide [1]. Hypertensive disorders are significantly associated with foetal growth restriction, low birth weight, spontaneous or iatrogenic preterm delivery in approximately 8-10% of cases [2], respiratory distress syndrome, cerebral palsy, and admission to neonatal intensive care [3].

Preeclampsia (PE) and eclampsia syndrome are two of the most significant hypertensive disorders that occur during pregnancy. PE involves impaired endothelial function, widespread arterial constriction, and a reduction in intravascular volume, including in the ocular region [4]. Ocular circulation serves as an indirect representation of cerebral haemodynamic owing to its embryological, anatomical as well as functional similarities with cerebral circulation.

There is a growing body of literature on ophthalmic artery Doppler as a predictive tool for pre-eclampsia and its effectiveness in assessing the severity of the condition. Nevertheless, the results from various studies on ophthalmic Doppler parameters to use and when to use during the different trimesters of pregnancy appear inconclusive. It remains uncertain whether these parameters are exclusive to PE, if they accurately reflect the severity of maternal disease, and if they could serve as indicators of adverse maternal as well as perinatal outcomes. Utilizing Doppler ultrasound to assess the ophthalmic artery during the third trimester of pregnancy can potentially predict PE development [4]. The ophthalmic artery provides an opportunity that is easily accessible for monitoring maternal cardiovascular changes, especially in women with hypertensive disorders of pregnancy. Magnetic Resonance Imaging (MRI) permits the investigation of intracranial blood flow dynamics during pregnancy; however, its use is limited by its high cost, lack of accessibility, and contraindications for individuals with ferromagnetic implants. Radiological imaging techniques like radionuclide imaging, catheter angiography, and computed tomography angiography, which are used to examine intracranial blood vessels, involve ionizing radiation. As a result, these methods pose potential risks to the foetus and are not recommended for use during pregnancy [5].

Transcranial Doppler ultrasound serves as a safe diagnostic tool for examining intracranial blood vessels. Although it delivers rapid results, its use is complicated because of the requirement of technical proficiency, which may lead to low spatial resolution [5]. Furthermore, transcranial Doppler imaging devices are rarely accessible in underprivileged countries. On the other hand, ophthalmic artery Doppler presents a cost-effective, precise, reproducible, non-invasive, and objective method that does not involve exposure to ionising radiation. Ophthalmic artery Doppler measurements can be easily obtained using regular ultrasound equipment without any influence from adiposity. The index reference ranges remain consistent across all pregnancy trimesters [6]. Utilizing ophthalmic artery Doppler is beneficial for screening and monitoring individuals with PE in low-resource settings, where there is a scarcity of technical equipment and inadequate compliance with antenatal care. This study was conducted to examine the possible variations in ophthalmic artery Doppler parameters between normotensive and hypertensive women during the third trimester of pregnancy.

Material and Methods

This prospective study was carried out in a tertiary care hospital. We randomly recruited 70 women as cases who had PE and 70 normotensive pregnant women as controls within the reproductive age group of 18-49 years between 29- and 40- weeks Gestational Age (GA) at the Department of Obstetrics and Gynecology, JSS Hospital, Mysuru, Karnataka, from January 2023 to December 2023. All subjects provided informed consent prior to participation. Permission and approval for this study were received from the ethics and research committee of the JSS Medical Hospital.

Pregnant women who were less than 29 weeks and more than 40 weeks of gestation, not-consenting, smokers, and those with orbital pathologies and maternal diseases before pregnancy, such as diabetes, chronic hypertension, and multiple pregnancies, were excluded from both groups.

All the subjects' age, clinical history, parity, and gestational age were recorded, and blood pressure was measured using an aneroid sphygmomanometer. To assess the ophthalmic artery Doppler, subjects were placed in supine position with their head tilted approximately 15^0 away from the examination side, and a 7.5 MHz linear transducer was used after a 10-minute rest period. A minimal quantity of gel was gently spread to the closed eyelid, and the transducer was positioned horizontally without exerting pressure on the eye to prevent any alterations in measuring the flow velocity. Color Doppler was employed, and the transducer was moved up and down until the ophthalmic artery was identified and positioned approximately 15 millimeters from the optic disc on the medial aspect of the optic nerve. The ultrasound beam's insonation angle was adjusted to less than 20^0, and the sample volume size was set to 2 millimeters. Subsequently, the spectral waveform was generated by switching on the pulsed wave and capturing 5 spectral waveforms of comparable shapes and sizes. Peak Systolic Velocity (PSV), End-diastolic Volume (EDV), Resistivity Index (RI), and Pulsatility Index (PI) were determined using auto-tracing to obtain an average measurement from the spectra obtained from both eyes.

Statistical Package for the Social Sciences (SPSS) Version 22.0 software (IBM Corporation, Armonk, NY, USA) was used to analyze the data. Descriptive statistics of the explanatory and outcome variables were calculated using means and standard deviations for quantitative variables and frequencies and proportions for qualitative variables. The Chi-square test was employed to evaluate the statistical relationship between categorical variables, and Student's t-test was utilized to assess the disparity in the mean of qualitative variables. All the tests were conducted at a significance level of 5 %.

Results

In total, 140 patients, comprising 70 PE and 70 normotensive patients were assessed. There were no significant variations in age of patients between the groups (p = 0.900). Most of the patients were aged between 26 and 35 years. The gestational period of the patients varied between 29 and 40 weeks. The PE group had more primigravida 47 (67.1%) than the control group 37 (52.9%). Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Arterial Pressure (MAP) were normal in the control group in 39 (55.7%), 38 (54.3%), and 49 (70%) patients, respectively, whereas SBP, DBP, and MAP were ⩾ 120, ⩾ 70, and ⩾ 90, respectively. Around 33 (47.1%) patients had severe preeclampsia in the PE group. This was statistically significant for parity ($\chi^2 = 5.71$, $p = 0.017$); term ($\chi^2 = 11.82$, $p = 0.001$); SBP ($\chi^2 = 62.06$, $p = 0.001$); DBP ($\chi^2 = 99.02$, $p = 0.001$) and MAP ($\chi^2 = 75.38$, $p = 0.001$) (Table 1).

Gestational age was higher in the control group (37.97 ± 1.79) than in the PE group (35.69 ± 3.25). The mean SBP, DBP, and MAP were found to be significantly higher in PE group - 150.97 ± 13.27, 99.83 ± 8.59, and 116.77 ± 9.25 as compared to the control group – 116.89 ± 4.75, 72.46 ± 5.06 and 87.27 ± 4.10 respectively (p =0.001) (Table 2).

Right PSV (32.01 ± 1.97), left PSV (31.60 ± 1.65), right PI (1.45± 0.14), left PI (1.44 ± 0.13), right RI (0.78 ± 0.06), left RI (0.75 ± 0.06) were significantly higher in the control group whereas right EDV (13.30 ± 2.17) and left EDV (13.05 ± 2.14) were significantly higher in the PE group (p = 0.001) (Table 3).

The PE group showed more emergency Lower Segment Caesarean Section (LSCS) – 43 (61.4%), and the control group showed higher vaginal delivery. The PE group had more female babies i.e. 37 (52.9%) and the control group had more male babies i.e. 39 (55.7%). Only 5 (7.1%) subjects had Intrauterine Devices (IUD) placed in the PE group. There was a statistically significant association between the mode of delivery (χ^2=17.21, p=0.001) and IUD (χ^2=5.18, p=0.023) (Table 4).

The mean weight of the babies was significantly higher in the control group (2.88 ± 0.49) than in the PE group (2.25 ± 0.83) (p =0.001) (Table 5).

Table 1: Distribution based on demographic characteristics and clinical findings

		Groups		Total	Chi-square	*p*
		PE	Control			
Age groups	**19 to 25 years**	22	22	44	0.211	0.900
		31.4%	31.4%	31.4%		
	26 to 35 years	45	46	91		
		64.3%	65.7%	65.0%		
	> 35 years	3	2	5		
		4.3%	2.9%	3.6%		
Parity	**Multi**	23	37	60	5.71	0.017*
		32.9%	52.9%	42.9%		
	Primi	47	33	80		
		67.1%	47.1%	57.1%		
Term / Preterm	**Preterm**	32	13	45	11.82	0.001*
		45.7%	18.6%	32.1%		
	Term	38	57	95		
		54.3%	81.4%	67.9%		

Continued...

		Groups		Total	Chi-square	*p*
		PE	Control			
SBP mmHg	**100 to 109**	0	4	4	62.06	0.001*
		0.0%	5.7%	2.9%		
	110 to 119	0	39	39		
		0.0%	55.7%	27.9%		
	⩾ 120	70	27	97		
		100.0%	38.6%	69.3%		
DBP mmHg	**60 to 69**	0	20	20	99.02	0.001*
		0.0%	28.6%	14.3%		
	70 to 79	0	38	38		
		0.0%	54.3%	27.1%		
	⩾ 70	70	12	82		
		100.0%	17.1%	58.6%		
MAP	**⩾ 90**	70	21	91	75.38	0.001*
		100.0%	30.0%	65.0%		
	79 to 89	0	49	49		
		0.0%	70.0%	35.0%		
HDP	**Gestational Hypertension**	14	0	14	-	-
		20%	0%	20%		
	Preeclampsia	22	0	22		
		31.4%	0%	31.4%		
	Severe PE	33	0	33		
		47.1%	0%	47.1%		
	Eclampsia	1	0	1		
		1.4%	0%	1.4%		

**Significant*

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, PE: Preeclampsia, HDP: Hypertensive disorders of pregnancy

Table 2: Baseline characteristics between the groups were compared using an independent sample t-test

	Groups	N	Minimum	Maximum	Mean ± SD	Mean Diff	*p*
GA	**PE**	70	28.2	40.3	35.69 ± 3.25	-2.27	0.001*
	Control	70	30.0	40.1	37.97 ± 1.79		
SBP	**PE**	70	130.0	178.0	150.97 ± 13.27	34.08	0.001*
	Control	70	108.0	126.0	116.89 ± 4.75		
DBP	**PE**	70	86.0	124.0	99.83 ± 8.59	27.37	0.001*
	Control	70	64.0	84.0	72.46 ± 5.06		
MAP	**PE**	70	101.0	140.0	116.77 ± 9.25	29.50	0.001*
	Control	70	79.0	97.0	87.27 ± 4.10		

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, PE: Preeclampsia, GA: Gestational age

Table 3: Quantitative parameters were compared between the groups using an independent sample t-test

	Groups	N	Minimum	Maximum	Mean ± SD	Mean Diff	*p*
Right PSV	**PE**	70	8.45	32.60	19.88 ± 6.98	-12.13	0.001*
	Control	70	28.30	37.50	32.01 ± 1.97		
Left PSV	**PE**	70	7.99	32.90	20.28 ± 7.24	-11.31	0.001*
	Control	70	28.40	36.40	31.60 ± 1.65		
Right EDV	**PE**	70	9.60	17.91	13.30 ± 2.17	4.57	0.001*
	Control	70	6.10	10.70	8.73 ± 1.09		
Left EDV	**PE**	70	9.3	17.3	13.05 ± 2.14	4.52	0.001*
	Control	70	6.2	10.6	8.53 ± 1.04		
Right PI	**PE**	70	0.56	1.34	1.01 ± 0.21	-0.43	0.001*
	Control	70	1.10	1.75	1.45 ± 0.14		
Left PI	**PE**	70	0.52	1.32	0.97 ± 0.20	-0.46	0.001*
	Control	70	1.21	1.73	1.44 ± 0.13		
Right RI	**PE**	70	0.42	0.73	0.59 ± 0.08	-0.91	0.001*
	Control	70	0.65	0.93	0.78 ± 0.06		
Left RI	**PE**	70	0.41	0.72	0.56 ± 0.08	-0.91	0.001*
	Control	70	0.60	0.87	0.75 ± 0.06		

PSV: Peak systolic velocity, EDV: End-diastolic volume, PI: Pulsatility index, RI: Resistivity index

Table 4: Distribution based on the mode of delivery, gender of the baby, and IUD

		Groups		Total	Chi-square	*p*
		PE	Control			
Mode of delivery	**Elective LSCS**	14	11	25	17.21	0.001*
		20.0%	15.7%	17.9%		
	Emergency LSCS	43	23	66		
		61.4%	32.9%	47.1%		
	Vaginal	13	36	49		
		18.6%	51.4%	35.0%		
Gender of baby	**Female**	37	31	68	1.02	0.31
		52.9%	44.3%	48.6%		
	Male	33	39	72		
		47.1%	55.7%	51.4%		
IUD	**No**	65	70	135	5.18	0.023*
		92.9%	100.0%	96.4%		
	Yes	5	0	5		
		7.1%	0.0%	3.6%		

LSCS: Lowersegment caesarean section, IUD: Intrauterine device

Table 5: Comparison of baby weight between the groups performed using an independent sample t-test

	Groups	N	Minimum	Maximum	Mean ± SD	Mean Diff	*p*
Weight (Kgs)	**PE**	70	0.60	4.20	2.25 ± 0.83	-0.62	0.001*
	Control	70	1.10	3.90	2.88 ± 0.49		

Discussion

Pregnancy-induced Hypertension (PIH) typically manifests in both maternal and foetal adverse effects. However, in some cases, it can present as a predominantly affecting either the mother or the foetus. The occurrence, development, and intensity of PE can vary significantly in a natural context, with unpredictable timing, intensity, and severity. The commonly cited explanation for the observed pathology is that inadequate transformation of spiral arteries and excessive oxidative stress in the placenta leads to a systemic inflammatory reaction, characterized by extensive damage to the endothelium, where the placenta is considered the primary pathogenic agent in this process [7]. Nevertheless, various studies argue that this condition is not just confined to the placenta, especially when there is no abnormal placental histology or poor foetal development evident [8]. Alternative hypotheses for this syndrome, particularly for certain phenotypes, propose the likelihood that specific maternal cardiovascular factors, such as pre-existing cardiac dysfunction, may cause placental malfunction due to maternal cardiovascular mal adaptation [9]. In this context, incorporating ophthalmic artery Doppler alongside uterine artery Doppler appears suitable, given its relevance to other suggested theories regarding the pathophysiology of PIH. Research conducted on PE patients consistently demonstrates lower PI and RI, along with elevated peak and flow velocity ratios, suggesting reduced cerebrovascular resistance and hence reduced orbitovascular resistance and increased orbital flow. In general, this suggests a consistent increase in pan-systolic blood flow velocities [10-11]. Given that a substantial portion of the disease burden is experienced during the third trimester, we conducted our study among women in this particular phase.

This study examined ophthalmic artery Doppler velocimetric indices in both normotensive pregnant women and those diagnosed with PE. There was no difference in the age of the patients between the PE and control groups. The patients' mean age in the study group reported by Hikima *et al*. was 25.81 ± 6.85 years [12]. In Nigeria, Yakasai and Bello [13] reported the mean age of 26.03 years, which was lower than that documented by Adokiye *et al*. [14] and Olatunji *et al*. [15] (29.02 ± 10.34 years). The age group with the highest proportion of patients (64.3%) in the severe PE group was between 26 and 35 years. This is higher than the percentages indicated by Adokiye *et al*. [14], where 50.53% of the patients were between 20 and 29 years old, and Kooffreh *et al*. [16], documented 42.4% in the age group of between 20 and 25 years. Among our PE subjects, 67.1% were primigravidas, while the remaining 47.1% were multigravidas. This finding aligns with previous research, which found a higher prevalence of PE among first-time mothers. In the control group, the mean gestational age (37.97 ± 1.79) was higher compared to PE group (33.18 ± 3.71), but there was no statistical significance noted. In contrast, according to Hikima *et al*. the mean gestational age of the control group (30.46 ± 4.47) was lower than that of the PE group (33.18 ± 3.71). Yakasai and Bello [13] noted that the gestational age for PE development was approximately 34 weeks and Kooffreh *et al*. [16] documented 34–38 weeks. A correlation between gestational age and the velocimetric indices measured in the control group was also established, and no notable alteration was observed in any of the Doppler parameters with the gestational age. This finding aligns with that of previous studies [15,17]. The mean peak systolic velocities in both the right and left ophthalmic arteries of the PE group were significantly lower than those in the control group. This aligns with the findings of Olatunji *et al*. [15] who conducted similar research in southwestern Nigeria and observed statistically significant decrease in PSV among women with PE compared to normal pregnant women. The mean PSV in the normotensive group was comparable to that reported by Olatunji *et al*. [18]. The discrepancy between these studies is likely attributed to variations in the prevalence of risk factors for PE among the different study populations.

This study documented a notable rise in the mean right as well as left end-diastolic volume in the PE group which aligns with results reported in other studies [12, 15]. Patients with PE were observed to have a higher level of diastolic blood flow compared to those with normal pregnancies. It is also noteworthy that a comparable increase in diastolic flow occurs in severe PE compared to mild-to-moderate PE. A statistically significant difference was observed between the right and left RI in PE pregnant women compared to those with normal pregnancies. A lower right RI (0.59 vs. 0.78, $p = 0.001$) and lower left RI (0.56 vs 0,75) were noted in PE pregnant women. These findings are in agreement with those reported by Olatunji *et al*. [18]. Severe hypertension in PE surpasses the autoregulatory limit, resulting in vasodilatation.

Additionally, endothelial dysfunction triggers higher systemic vasodilators secretion such as nitric oxide, and decreases the secretion of vasoconstrictors. As a result, orbital hyperperfusion occurs due to reduced impedance to ocular blood flow.

A significantly lower PI in women with PE ($p = 0.001$) was noted in this study. This finding is aligned with the results reported in other studies [15, 19]. This study also revealed a significantly higher number of emergency LSCS procedures in the PE group compared to the control group. Sarno *et al*. demonstrated that the ophthalmic artery Peak Ratio (PR) at 35-37 weeks of gestation could predict subsequent delivery with PE with a detection rate of 50% if PE happens within 3 weeks after assessment [20]. Our research sought to establish whether ophthalmic artery Doppler was primarily utilized to evaluate disease severity rather than to forecast it. A prior study corroborated the findings of lower impedance and increased intraocular pressure. The study focused on fundus examination and discovered that only a small number of women with PE exhibited abnormal fundoscopic results. Thus, it was suggested that ophthalmic artery Doppler could be a valuable diagnostic tool for identifying women at risk of developing PE and its associated complications [21].

This suggests that fundoscopy which was traditionally considered the primary tool for reflecting cerebrovascular hemodynamics, could potentially be supplanted by ophthalmic artery Doppler. Gurgel and colleagues investigated the effectiveness of ophthalmic artery Doppler and uterine artery Doppler in detecting early PE in the first trimester of pregnancy. Their findings revealed that both methods had a detection rate of 67%, emphasizing the importance of monitoring cardiovascular and systemic vascular changes in pregnant women that may occur prior to the onset of the disease [22]. In a meta-analysis conducted by Kalafat *et al*., it was found that ophthalmic artery Peak Systolic Velocity (PSV) demonstrated only modest performance in predicting early-onset or late-onset PE. The ophthalmic artery PI did not show significant predictive value. Only a

PR above 0.65 was predictive of early-onset PE, with an Area Under the Curve (AUC) of 0.67 for early onset and 0.57 for late-onset PE [23].

In a study conducted by Sapantzoglou *et al*. during the second trimester, the potential of ophthalmic artery Doppler and other biomarkers in predicting PE at 19-23 weeks of gestation was assessed. The results indicated that a higher PSV and PR were effective in predicting preterm PE, both as individual measures and in combination with other biomarkers [24]. Recently, Matias and colleagues found that hypertensive complications during pregnancy were predicted independently by the PSV of the ophthalmic artery, even between the 20th and 28th week of gestation [25]. A recent large-scale investigation of ophthalmic artery Doppler during both the first and second trimesters revealed that predicting PE solely with PR was superior to using a test that combined maternal parameters, MAP, uterine artery PI, and biomarkers. This improvement led to increased detection rates, rising from 84.9% to 89.8% in preterm pregnancies and from 43.0% to 51.2% in term pregnancies, with a false-positive rate of 10% [26]. In another study, researchers observed that despite normalization of blood pressure, ophthalmic artery Doppler examinations performed up to 90 days postpartum in preeclamptic postnatal women did not return to the levels seen in normotensive postnatal controls. This has raised the question of whether these alterations have any connection to the subsequent emergence of long-term complications [27]. In a study by Oliveira *et al.* the effects of magnesium sulphate on preeclamptic patients were examined, revealing that ophthalmic artery PR decreased while RI and PI increased. This suggests that magnesium sulphate increased the ocular artery's resistance to flow, which in turn may have led to a decrease in cerebral perfusion after use [28].

Researchers discovered that, despite following clinical guidelines to lower blood pressure in PE cases, cerebral perfusion pressure remained elevated, suggesting that existing clinical tests for evaluating the risk of cerebrovascular disease are inadequate. Additionally, it was observed that different antihypertensive agents have varying effects on cerebral perfusion pressure and cerebral blood flow. Therefore, further research in this area is warranted. This study emphasized the necessity for larger studies to incorporate ophthalmic artery Doppler into existing clinical guidelines. However, it acknowledged the limitations posed by its small sample size.

Conclusion

This study illustrated the utility of ophthalmic artery Doppler in patients with PE and those at risk of developing this condition. These findings indicate a reduction in PSV and EDV, as well as a decrease in EDV, PI, and RI in patients with PE. These variations are indicative of increased cerebral perfusion, which leads to clinical manifestations of PE. Ophthalmic artery Doppler could potentially be employed to identify individuals who are at risk of developing PE, thereby enabling enhanced care and preventing potential complications associated with the disorder. This approach may ultimately contribute to a reduction in maternal mortality rates. Larger studies are needed to predict adverse maternal outcomes using ophthalmic artery Doppler imaging.

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