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Original Research Article

Comparison of ophthalmic artery Doppler indices among hypertensive and normotensive pregnant women in third trimester: association with perinatal outcomes

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ABSTRACT

Background: In this study, we compared ophthalmic artery Doppler indices between normotensive and hypertensive pregnant women in third trimester and then evaluated if the alterations in ophthalmic artery doppler indices were seen in all the types of hypertension in pregnancy or confined to preeclampsia. Further we tried to see correlation of ophthalmic artery Doppler indices with perinatal outcomes in terms of fetal growth restriction (FGR), prematurity, neonatal intensive care unit admission (NICU) and maternal outcomes and tried to arrive at mean values of ophthalmic artery Doppler indices to predict adverse outcomes.

Methods: 50 hypertensive and 50 normotensive pregnant women were recruited in third trimester. A thorough history about hypertension was taken, obstetric scan was done to know estimated fetal weight, and doppler of umbilical, middle cerebral artery, uterine arteries was done. Simultaneously maternal ophthalmic artery Doppler readings were taken, women were followed up after delivery and perinatal outcomes were recorded.

Results: Comparison of mean values of ophthalmic artery doppler parameters in women with and without hypertension showed statistically significant differences with respect to the peak systolic velocity 2 (PSV2), PI (pulsatility index), RI (resistivity index) and peak ratio (PR) ($PR=PSV2/PSV1$). Significant difference was found only in PR value in preeclampsia group compared to other subgroups of hypertension. In the hypertension group complicated with FGR the mean peak ratio=0.8 whereas in the hypertension group requiring preterm delivery the mean peak ratio=0.78, and in the hypertension group requiring NICU admission the mean peak ratio=0.81. At ophthalmic artery PR cut off ≤ 0.725 , the sensitivity and specificity were 76% and 65% respectively to predict FGR.

Conclusions: Pregnancy complicated by hypertension showed alterations in ophthalmic artery Doppler indices. Among the subgroups of hypertension, ophthalmic artery PR was the best index for discriminating preeclampsia from other types and it was significantly higher in hypertensive pregnant women who had adverse perinatal outcomes. Ophthalmic artery PR has almost similar performance as uterine artery PI in indicating FGR in our study. It could also indicate maternal disease severity such as hypertensive crisis requiring ICU admission, the study number was small.

Keywords: Ophthalmic artery Doppler, Hypertension, Severe preeclampsia, Peak systolic velocity, Peak ratio, Uterine artery Doppler

INTRODUCTION

There is evolving literature on ophthalmic artery Doppler to predict preeclampsia and its utility as a measure of severity of preeclampsia. But there are conflicting results about which ophthalmic Doppler parameter to choose and in which trimester of pregnancy its best applied. It's also unclear if these parameters are confined to preclampsia alone, if these doppler parameters are reflective of maternal disease severity and if they could indicate adverse maternal and perinatal outcomes.

With a reported frequency of roughly 10% globally and 9% in India, pregnancy complicated by hypertension is one of the major causes of perinatal morbidity and deaths. About 3-5 percent of pregnant women get preeclampsia.¹ Preeclampsia is one of the illnesses that fall under the category of pregnancy hypertensive disorders, along with eclampsia, gestational and chronic hypertension as per the. Apart from eclampsia, hypertension in pregnancy can lead to short and long-term neurological problems, cardiovascular and renal complications in the mother while the fetus is at risk of prematurity, growth restriction, abruption, stillbirth, and neonatal death.^{2,3}

It is well known that the performance of uterine artery doppler as an isolated test was insufficient and better screening performance for preclampsia could only be obtained when they were integrated with additional biophysical and biochemical markers in a multiparametric approach.^{4,5} The practical use of this screening test involves using aspirin as a treatment which, when started earlier than 16 weeks, is linked to a much lower risk of emerging early-onset preeclampsia, fetal development restriction, and premature delivery. But alternative or add-on methodologies not only to predict PIH but also to assess disease severity, to assess response to antihypertensive therapy or magnesium sulfate, and to predict perinatal complications are still to be studied rather than relying on the currently used symptoms of impending eclampsia, which are sometimes non-specific. Particularly predicting neurological problems including eclampsia, which is thought to occur as a consequence of loss of cerebral autoregulation leading to posterior reversible encephalopathy syndrome can be difficult because it is known that the blood pressure level during pregnancy at which cerebral deregulation takes place is uncertain and variable.^{6,7} Doppler investigations of the ocular arteries have been utilized to manage disorders that impact the cerebral vasculature because the ocular circulation represents the condition of the hemodynamic cerebral flow owing to its anatomical, functional, and embryological similarities.⁸ Therefore, identifying cerebral overflow with ophthalmic artery Doppler ultrasound in the context of PIH may be a sign of the risk of cerebral problems. Also it is understood that Doppler of other larger intracranial vessels such as middle cerebral artery do not reflect preclamptic changes making ophthalmic artery sole investigational tool in Doppler.⁹

Ophthalmic artery Doppler can be assessed using conventional ultrasound device in a typical obstetric setting. The drawbacks with the usage of CT and MRI due to their inherent limitations of not being easily available bedside in an emergency setting even in a high-end tertiary setup turns heads towards more easily available investigating modalities. Furthermore, ocular Doppler has been shown to be an accurate technique, unlike uterine artery Doppler assessment, as it does not suffer from the methodological issues related to the space-occupying effect of a gravid uterus and/or maternal obesity.

METHODS

The trial was performed in a tertiary mother and child hospital in the north coastal region of Andhra Pradesh, India between July 2021 to May 2022. All of the recruited women provided written consent for the study, and the institution's ethics committee approved it. 118 pregnant females were recruited in the third trimester, out of which 63 were hypertensive and 55 were normotensive. Exclusion criteria included other co-morbidities, those who have taken magnesium sulfate before starting of the study, those in whom delivery occurred earlier due to other reasons such as preterm labour and preterm premature of membranes, multiple pregnancy. After applying exclusion criteria, there were 50 hypertensive women in the study group. There were 23 preclampsia out of which 14 were severe preclampsia, 9 were mild preclampsia, 18 were gestational hypertension, 9 were chronic hypertension.

The following details were gathered and put into a proforma: sociodemographic information, the date and gestational age, previous obstetric and medical information, and a history of the hypertension in the present pregnancy and results of blood and urine investigations that were performed. On the scanning day, BP was taken after 5 minutes of rest before examining the Ophthalmic artery Doppler, and the mean arterial pressure was computed with the method,

mean arterial pressure (MAP)=(2×diastolic pressure)+systolic blood pressure.

Their maximum blood pressure record since they were diagnosed with PIH was noted, and the patient was asked if she was administered magnesium sulfate, liver and renal function tests, platelet counts and urine albumin tests were verified before ascertaining the type of PIH, and they were asked if they had symptoms suggestive of imminent eclampsia like epigastric pain, headache, photopsia (light flashes) as well as photophobia (light sensitivity). Patients were deemed to be preclamptic when their proteinuria was measured at or above 1 on a dipstick and their blood pressure was less than 140/90 mm Hg. When any of the following symptoms were present, severe preclampsia was determined to be present: (a) blood pressure \geq 160/110 mmHg; (b) proteinuria 3+; (c) urinary output volume <500 ml in 24 hours; (d) pulmonary oedema; and (e) symptoms of imminent eclampsia. The women underwent

transabdominal ultrasound examination with color-flow/pulsed Doppler of both uterine arteries at their apparent intersection with the internal iliac artery. The sample volume was placed to occupy the entire diameter of the Uterine artery at 1 cm distal from that site and mean uterine artery PI was obtained. Further an obstetric ultrasound was done and estimated fetal weight, umbilical, middle cerebral artery Doppler indices were recorded. The ophthalmic artery was then examined in line with predetermined procedures.¹⁰ A still picture was captured from three to six successive blood flow waveforms that were comparable in size and shape. The flow-velocity waveforms exhibited a high maximal systolic peak (PSV1) and a second systolic peak (PSV2) and a low diastolic velocity. PSV1, PSV2, EDV, RI, and PI were all computed. The PR was described as the variation between the PSV2 and PSV1 and calculated as PSV2/PSV1. An average of two to three minutes were needed to analyze the ophthalmic Doppler. ANOVA (analysis of variance) was used to assess the indices of PSV1, PSV2, EDV, RI, and PI. It was deemed to be significant if p value was <0.05. Values are presented as mean±standard deviation (SD). Scans were performed using Voluson GE E8 BT-19 equipment (high-resolution, Austria) with a 7.5 MHz linear transducer by a single operator who underwent training in fetal medicine. An ophthalmologist who is well versed in doing ophthalmic artery Doppler participated in the study by supervising initial scan images.

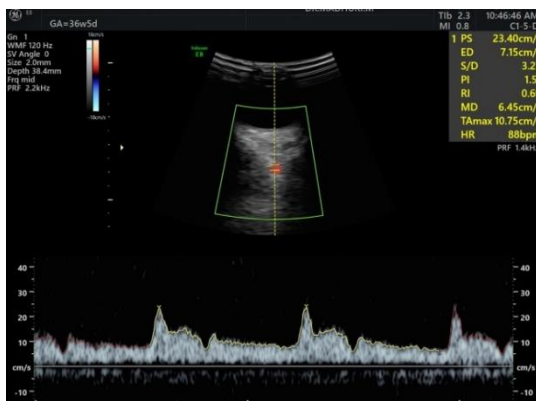


Figure 1: Representative image of ophthalmic artery doppler waveform in a normotensive woman.

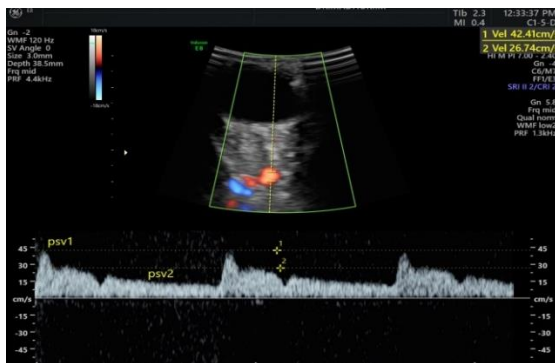


Figure 2: Representative image of ophthalmic artery Doppler waveform in a hypertensive woman.

Pregnancy outcome data such as gestational age at which patient was delivered, birth weight, and if there was any need for neonatal intensive care unit (NICU) admission, was obtained later from case sheets. The representative images of ophthalmic artery doppler taken (Figure 1 and 2).

RESULTS

To compare mean values of the of the ophthalmic and uterine arteries Doppler parameters in 50 women with hypertension and 50 normotensive women, ultrasound of the uterine and Ophthalmic arteries doppler was performed in pregnant women in third trimester of pregnancy. The demographic variables and results obtained were tabulated (Table 1).

Between women with hypertension and normotensive women: PI, PSV2, RI, and PR indicated statistically significant differences when the ophthalmic artery doppler mean values were compared. The values obtained were as follows: ophthalmic artery PI-significant (t value 4.77, p value 0.00001), ophthalmic artery PSV2-significant (t value -2.918, p value 0.0021), peak ratio-significant (t value -6.43, p value 0.0001), ophthalmic artery RI-significant (t value 1.69, p value 0.04), ophthalmic artery PSV1-not significant (p value 0.875), ophthalmic artery EDV-not significant (t -1.61, p value 0.054).

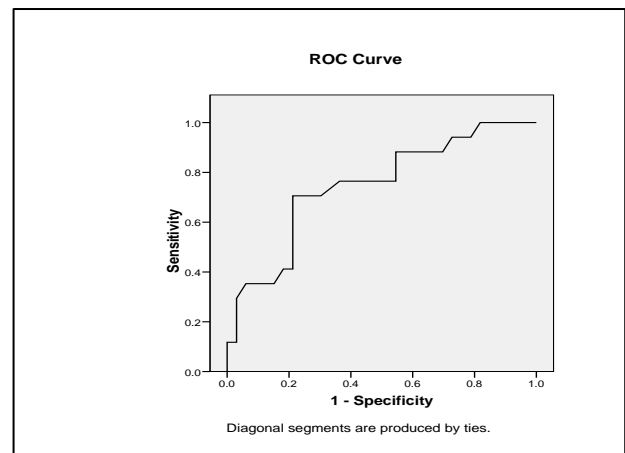


Figure 3: ROC curve to show ophthalmic artery PR sensitivity and specificity for FGR.

Between different subgroups of hypertension, mean values of different ophthalmic artery Doppler indices were compared and the results were tabulated (Table 2). Peak ratio among subgroups: significant (p=0.00361). P value is (0.02) between preclampsia as a whole and gestational hypertension, p value is (0.02) between severe preclampsia and gestational hypertension and p value is (0.001) between preclampsia and chronic hypertension making it statistically significant. PSV1 among subgroups: not significant (p=0.529), PSV2 among subgroups: not significant (p=0.935), RI (p=0.22 not significant), PI (p=0.31) not significant, EDV (p=0.17) not significant

among subgroups of hypertension. In comparison to the other groups, there were no considerable variations in the PSV1, PSV2, pulsatility index, resistive index, or EDV in severe preeclampsia women. Only the peak ratio significantly differed from other groups in patients with severe preeclampsia.

PR in hypertensive women with adverse perinatal outcomes such as FGR, prematurity, NICU admission and maternal ICU admission was compared individually with PR of those hypertensive women where there were no adverse outcomes. Because there could be a minimal element of subjectivity among obstetricians in deciding when to terminate the pregnancy, and when to admit in ICU, we have mainly concentrated on correlation of PR with FGR where there is no chance for subjectivity. The results are as follows.

There were total 17 FGR cases among the 50 hypertensive women. Among those FGR uterine artery PI was high in 13 and normal in 4 cases. Among those 33 cases with no FGR, in 25 cases uterine artery PI was normal and uterine artery PI was high in 8 cases, making the sensitivity, specificity, PPV of uterine artery to be 76%, 77% and 61% respectively. AUC for uterine artery PI was 0.73. To assess the performance of ophthalmic artery PR for predicting FGR, ROC curves are obtained for different cut offs. Ophthalmic artery PR was significant (p=0.001) and AUC was 0.75. At ophthalmic artery PR cut off ≤ 0.725 , the sensitivity and specificity were 76% and 65% respectively to predict FGR (Figure 3). In hypertension group with FGR, mean PR=0.8 (SD 0.25) whereas in those with no FGR in the hypertensive group the mean PR=0.68 (SD 0.4) which is a significant difference (p value -0.0008).

Table 1: Comparison of demographic variables, ophthalmic and uterine arteries Doppler parameters in women with hypertension and normotensive women.

Parameters	Hypertensive group	Normotensive group
MAP on day of scan \pm SD	103 \pm 9	86.4 \pm 8.8
Body mass index (BMI)	30.5 \pm 5.3	29 \pm 5.1
Gestational age at recruitment in weeks	33.7 \pm 3.2	34.5 \pm 2.6
Age	27.9 \pm 3.2	26.9 \pm 4
Mean uterine PI	1.05 \pm 0.38	0.65 \pm 0.21
ophthalmic artery PI	1.3 \pm 0.38	1.7 \pm 0.33
Ophthalmic mean PSV1	42.3 \pm 23	38.68 \pm 17
Ophthalmic mean PSV2	29.6 \pm 14.5	22.25 \pm 9.8
Ophthalmic mean EDV	11.35 \pm 4.8	9.83 \pm 2.9
Ophthalmic mean RI	0.66 \pm 0.1	0.69 \pm 0.09
Ophthalmic PR	0.72 \pm 0.12	0.57 \pm 0.1
Fetal weight at delivery (kilograms)	2.2 \pm 0.8	2.5 \pm 0.9
Gestational age at delivery in weeks	35.5 \pm 3	39 \pm 2.1

Table 2: Among different subgroups of hypertension, comparison of values of different ophthalmic artery Doppler indices.

Parameters	Mild preclampsia	Severe preclampsia	Preclampsia	Gestational hypertension	Chronic hypertension
Uterine artery PI	1.24 \pm 0.3	1.2 \pm 0.35	1.2 \pm 0.34	0.94 \pm 0.39	0.92 \pm 0.5
Ophthalmic PSV1	41.2 \pm 19	35.9 \pm 20	37 \pm 19.7	41.4 \pm 24	51.14 \pm 25
Ophthalmic PSV2	31.74 \pm 13	29.5 \pm 11	30.5 \pm 12	27.8 \pm 10	30.6 \pm 12
Ophthalmic PR	0.76 \pm 0.1	0.83 \pm 0.1	0.8 \pm 0.1	0.69 \pm 0.11	0.63 \pm 0.07
Ophthalmic RI	0.6 \pm 0.1	0.64 \pm 0.1	0.63 \pm 0.1	0.677 \pm 0.1	0.685 \pm 0.1
Ophthalmic PI	1.13 \pm 0.3	1.26 \pm 0.3	1.22 \pm 0.3	1.44 \pm 0.39	1.36 \pm 0.5
Ophthalmic EDV	15.4 \pm 5	11.1 \pm 4.5	12.5 \pm 4.8	10.9 \pm 3.5	9.5 \pm 3

Similarly, in hypertension group requiring preterm delivery of <37 weeks, mean PR=0.78 (SD 0.29) whereas in the hypertensive group not requiring preterm delivery mean PR=0.69 (SD 0.41) which is a significant difference (p value 0.0055). In hypertension group requiring NICU admission, mean PR=0.81 (SD -0.24) whereas in those not requiring NICU admission, mean PR=0.68 (SD 0.39) which is a significant difference (p value=0.0002). In the

hypertension group with maternal adverse effects in the form of hypertensive crisis/imminent eclampsia symptoms requiring ICU admission, the mean PR=0.93 (SD 0.25) whereas in those women with hypertension where maternal condition is stable, the mean PR is 0.8 (SD 0.4) which is a significant difference (p value=0.0001).

DISCUSSION

PIH usually manifests as a combination of both maternal and fetal adverse effects though at times it can present as a predominantly maternal syndrome or a fetal syndrome. The natural background of preeclampsia is highly variable in terms of timing of onset, degree, and severity of progression. The most widely recognized pathophysiological explanation for this heterogeneity, is that insufficient spiral artery remodeling and placental oxidative stress cause a systemic inflammatory response with widespread endothelial dysfunction, wherein the placenta was thought to be a main pathogenic agent.^{11,12} However, several studies contend that this condition is not only a placental disease, particularly when neither aberrant placental histology nor poor fetal development is present.¹³ Alternative theories for this syndrome, at least in certain phenotypes, include the possibility that certain maternal cardiovascular variables, such as pre-existing cardiac dysfunction, might result in placental malfunction related to maternal cardiovascular maladaptation.^{14,15} In this background, utilizing ophthalmic artery Doppler also along with uterine artery doppler seems appropriate as it was relevant to the other proposed theories of PIH pathophysiology also. Studies from preeclampsia patients have nearly always shown lower PI and RI together with higher peak and flow velocity ratios, indicating lowered cerebrovascular resistance. Overall, this showed continuously higher pan-systolic blood flow velocities.^{16,17}

As much of the disease burden occurs in third trimester, we studied women in third trimester. In a recent study by Sarno et al ophthalmic artery PR as late as at 35-37 weeks' gestation was shown to predict subsequent delivery with preeclampsia with 50% detection rate, if this occurred within 3 weeks after assessment.¹⁸ In our study, we wanted to know in third trimester, if the application of ophthalmic artery Doppler was mainly on assessing disease severity rather than prediction of the disease.

Lower impedance and higher intra ocular pressures were also confirmed in another study which looked at fundus examination and showed that abnormal fundoscopic findings were observed in only a few preeclamptic women and hence ophthalmic artery Doppler could be a useful add on method in identifying those women who were likely to suffer preeclampsia and its complications.¹⁹ This points out that fundoscopy which traditionally was thought to be the main tool to reflect haemodynamics of cerebrovasculature may be replaced with ophthalmic artery Doppler.

In a study by Gurgel et al ophthalmic artery Doppler and uterine artery Doppler were compared and found that ophthalmic artery PSV1 and uterine artery PI both had a similar detection rate of 67 percent for early preeclampsia in the first trimester, throwing light on the timing of cardiovascular and systemic vascular variations in pregnant females that may occur before the clinical onset of this illness.²⁰ In a meta-analysis by Kalafat et al ophthalmic artery

PSV1 performed only modestly in predicting early onset or late onset preeclampsia, ophthalmic PI was not significant, and only peak ratio above 0.65 was predictive of early onset preeclampsia with AUC 0.67 for early onset and 0.57 for late onset preeclampsia.²¹ In another second trimester investigation by Sapantzoglou et al ophthalmic artery Doppler in combination with other biomarkers in prediction of pre-eclampsia at 19-23 weeks gestation was studied and they showed that it was a higher PSV2 and PR that were helpful for predicting particularly preterm preeclampsia, both on its own and in combination with other biomarkers.²² More recently, the Matias group discovered that hypertensive pregnancy complications were independently predicted by the PSV2 of the ophthalmic artery even between 20 to 28 weeks.^{23,24} A recent large scale investigation on ophthalmic artery Doppler in both the first as well as second trimesters found that PR alone predicted preeclampsia better than by a test combining maternal parameters, MAP, uterine artery PI and biomarkers improving detection rates from 84.9% to 89.8% in preterm and from 43.0% to 51.2% in term pregnant women at a false positive rate of 10%.²⁵

In a study in preclamptic postnatal women, where serial ophthalmic artery Doppler exams were performed up to 90 days postpartum showed that despite the normalization of blood pressure, these changes did not fully return to the levels seen in normotensive postnatal controls and raised whether these alterations have any connection to the subsequent emergence of long term problems.²⁶ In a report by Oliveira et al the impact of magnesium sulfate on preclamptic patients was investigated and found that ophthalmic artery PR was decreased while RI and PI increased meaning it increases ocular artery's resistance to flow and indirectly pointing to a fall in cerebral perfusion following usage.²⁷ It was found that in preeclampsia even when blood pressures were brought down as per clinical recommendations, cerebral perfusion pressure remained elevated pointing out the lacunae of the currently used clinical tests for assessing the risk of cerebrovascular disease. Also, it was noted that there is a difference in the effects of various antihypertensive agents on cerebral perfusion pressure and cerebral flow hence requiring research in this area.

In our study we found that PR was the only parameter even in third trimester to be altered significantly in preeclampsia and that it also indicated few adverse perinatal outcomes.

Studies though had conflicting results in terms of which ophthalmic artery Doppler index performed better among PSV1, PSV2 and PR, overall, these studies might represent increase in pansystolic velocities in ophthalmic artery among hypertensive women. The need for further larger studies to integrate ophthalmic artery Doppler into existing clinical guidelines is sought through this study.

Limitations of the study include small sample size. We could not arrive at a PR value by which we could predict

eclampsia as none of the women fortunately had eclampsia in the study population.

CONCLUSION

Ophthalmic artery of the eye Doppler is an objective method for evaluating the mother's hemodynamic circulation and offers a view into the intracranial environment. Pregnant women with preeclampsia had over-perfusion according to ophthalmic artery Doppler imaging. The best measure for differentiating between preclampsia from other subgroups of hypertension was the peak ratio. In severe preclampsia, this peak ratio was still higher. It was also significantly higher in women who had adverse perinatal outcomes such as FGR, prematurity, NICU admission, maternal adverse outcomes. Ophthalmic artery could indicate FGR and its performance is comparable to uterine artery doppler. Though the number of women who had imminent eclampsia, hypertensive crisis requiring ICU admission was small, ophthalmic artery PR was highest among these women. Larger studies would be needed to be able to predict maternal adverse outcomes by ophthalmic artery Doppler.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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