International Journal of Reproduction, Contraception, Obstetrics and Gynecology
*Adlakha E et al. Int J Reprod Contracept Obstet Gynecol. 2024 Dec;13(12):3691-3701*
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20243606

**Original Research Article**

# Predictive value of ophthalmic artery doppler in pre-eclampsia development

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**Received:** 24 October 2024
**Revised:** 20 November 2024
**Accepted:** 21 November 2024

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## ABSTRACT

**Objective:** To evaluate the predictive value of maternal ophthalmic artery Doppler parameters, both independently and in combination with uterine artery pulsatility index (UtA-PI) and mean arterial pressure (MAP), in forecasting pre-eclampsia (PE) development.
**Methods:** This prospective observational study involved women at 19-23 weeks' gestation. Maternal demographics, medical history, ultrasound for fetal anatomy and growth, and Doppler measurements of ophthalmic artery flow velocities (PSV1, PSV2, PSV ratio) along with MAP and UtA-PI were assessed.
**Results:** The incidence of PE was 9.4%. Women with PE were older (35.8 vs. 32.3 years, $p<0.01$). Seventy-five percent developed early-onset PE. Mean UtA-PI was higher in PE cases (1.91 vs 1.27, $p=0.03$). UtA-PI showed good predictive value with 83.3% sensitivity and 68.7% specificity (accuracy: 76%). Ophthalmic artery parameters, particularly PSV2 (27.54 vs. 23.46, $p<0.01$) and PSV ratio (0.8 vs. 0.61, $p<0.01$), were significantly higher in PE cases. These parameters had sensitivity and specificity of 83.3%/58.3% (PSV2) and 83.3%/61.7% (PSV ratio), respectively. Combined ophthalmic artery Doppler parameters showed strong predictive value (AUC 0.832), with sensitivity 58.3%, specificity 90.4%, and accuracy 87.4%. Adding uterine and ophthalmic artery Doppler parameters increased accuracy to 91.3%. The combination of MAP, UtA-PI, and ophthalmic Doppler showed the highest accuracy (97.6%, AUC 0.969) with sensitivity 91.7% and specificity 98.3%.
**Conclusion:** Ophthalmic artery PSV ratio is a promising predictor for PE development, warranting further validation in larger studies.

**Keywords:** Ophthalmic artery doppler, Uterine artery doppler, Prediction of pre-eclampsia, Mean arterial pressure pre-eclampsia

## INTRODUCTION

Pre-eclampsia is a pregnancy specific hypertensive disease with multisystem involvement. A WHO secondary analysis in low and middle-income countries reported the incidence of preeclampsia to be in the range of 2–15% in India.[1] An ability to accurately predict this condition would enable better treatment facilities for pregnant women at high risk of developing pre-eclampsia. Pre-eclampsia (PE) being a hypercoagulable state is characterized by abnormal vascular response to placentation, endothelial dysfunction and increased systemic vascular resistance. The development of pre-eclampsia is hypothesized to be by deficient spiral artery remodelling and placental oxidative stress due to inadequate perfusion which results in widespread endothelial dysfunction along with generalized arterial constriction and decreased intravascular volume including to the ocular areas.[2] Early screening for pre-eclampsia may allow vigilant antenatal surveillance and appropriate timing of delivery in order to avoid serious sequalae. Traditionally maternal characteristics, uterine artery

doppler and biochemical indices have been used as predictive models for pre-eclampsia. However, none of them have been prognostically accurate. Due to moderate prognostic accuracy of clinical variables, current studies worldwide aim at identifying new predictors that can increase the ability to predict and identify women at risk of developing pre-eclampsia. Early identification of women at risk of development of pre-eclampsia is crucial to reducing maternal and perinatal morbidity and mortality. It allows for closer monitoring and the institution of prophylactic and therapeutic measures.

As there are embryological, anatomical and functional similarities in ocular and cerebral circulation, ocular circulation emulates the status of the hemodynamic cerebral circulation. Doppler studies of the ocular vessels are now being evaluated to manage diseases like pre-eclampsia that affect the cerebral vasculature.[3] The ophthalmic artery, which is the first branch of the internal carotid artery, is an easily accessible vessel for Doppler assessment that provides information on the less accessible intracranial circulation. Cross-sectional studies have reported that in pregnancies with pre-eclampsia (PE), compared to normal pregnancies, there is a decrease in impedance to flow and an increase in flow velocity in the ophthalmic arteries. There is also some evidence that development of pre-eclampsia is preceded by a decrease in impedance to flow in the cerebral circulation.[4]

Doppler is a non-invasive method for evaluation of feto-placental circulation without any disturbance to pregnancy. Assessment of ophthalmic artery doppler at 19-23 weeks identifies the high-risk group for development of early PE. While several studies are being done to study ophthalmic artery doppler as a screening tool for pre-eclampsia and fetal growth restriction in selected population, its role is still under evaluation. Different sensitivities are obtained depending on the type of Doppler indices used, the sampling site, the definition of different abnormal ophthalmic artery indices, gestational age of assessment and different end points.

Objectives of the study were to determine the prognostic value of ophthalmic artery Doppler velocimetry in pregnancy with respect to the occurrence of Pre-eclampsia and to compare the efficacy of ophthalmic artery doppler with uterine artery doppler in the prediction of pre-eclampsia.

## METHODS

### *Study site*

Study conducted at Jehangir hospital, Pune, Maharashtra, India.

### *Study population*

A total 127 registered antenatal cases, greater than 18 years, who delivered at this institute were selected.

### *Study design*

It was a prospective observational study.

### *Study duration*

Study conducted from 1st April -31st December 2023

### *Sample size estimation*

Sample size was determined by using the effect sizes from the previously published study.

Sample size was determined by using the effect sizes from the previously published study 5 and with the help of following formula:

$$n = \frac{(Z\alpha/2)^2 \times \text{Sensitivity} (1-\text{Sensitivity})}{d^2 \times \text{Prevalence}}$$

Sn = 0.610 (61.0%) (Published estimate of sensitivity)

Prev = 0.50 (50.0%) (Assumed prevalence),

Zα = 1.96 (Standard normal score at 95% confidence interval),

d = 0.12 (12.0%, margin of error).

n = 1.96^2×0.610×0.390 / (0.50×0.12^2) = 126.93.

Thus, the sample size calculated was 127.

The study was commenced after approval of ethics committee of the institution. This prospective observational study was conducted on eligible women. All women attending OPD at Jehangir hospital from 1st April -31st December 2023 and fulfilling the inclusion criteria were enrolled in the study. A written informed consent was obtained.

### *Inclusion criteria*

This included all women booked between 19-23 weeks at Jehangir Hospital with age>18 years.

### *Exclusion criteria*

This included smokers, patient on local or systemic antihypertensive drugs and refusal to consent.

All women who registered at Jehangir hospital and fulfilled the inclusion criteria were enrolled in the study. Informed consent was obtained from them before the study participation. A detailed history was taken including maternal age, menstrual history, obstetric history with age at marriage, consanguinity, parity, inter pregnancy interval and outcome of each previous pregnancy. relevant past and

family history, socioeconomic and dietary history. High risk factors like maternal age 35 years or older, pre pregnancy body mass index greater than 30, nulliparity, assisted reproductive technology, multifetal gestations, chronic hypertension, pregestational diabetes, gestational diabetes, thrombophilia, systemic lupus erythematosus, antiphospholipid antibody syndrome, kidney disease, obstructive sleep apnea, pre-eclampsia in a previous pregnancy.

General examination including height, weight, booking BMI and blood pressure were noted. Ongoing medications were documented. Patients were diagnosed as preeclamptic when they had a systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure or systolic blood pressure of 160 mmHg or more or diastolic blood pressure of 110 mmHg and proteinuria 300 mg or more per 24-hour urine collection ,protein/creatinine ratio of 0.3 or more, dipstick reading of 2+or in the absence of proteinuria, new-onset hypertension with any one of following new onset of thrombocytopenia (platelet count less than 100x109/l), renal insufficiency or serum creatinine concentrations greater than 1.1 mg/dl, a doubling of the serum creatinine concentration in the absence of other renal disease, impaired liver function (elevated blood concentrations of liver transaminases to twice normal), pulmonary edema, new-onset headache unresponsive to medication and not accounted for by alternative diagnoses, visual symptoms.

Mean arterial pressure was measured at the time of recruitment using validated automated devices with a standardized protocol. Mean uterine artery PI was recorded at NT scan at 11-13+6 weeks of gestation. An anomaly scan was performed at 19-23 week. At this time ophthalmic artery doppler was performed.

The ophthalmic artery was sampled by a linear array of frequency 9-1 MHz. Sample gate was placed 1.5 cm behind optic disc and medial to optic nerve, angle of insonation <20-degree, sample gate 2 mm, depth-3-4.5 cm, wall motion frequency 60 Hz, pulse repetition frequency - 125 kHz, 3 to 5 consistent cardiac cycles. Performance of screening twice from each eye was done. Ophthalmic artery peak systolic velocities 1 and 2 (PSV1, PSV2) and pulsatility index PI were noted. Flow velocity waveforms from the left and right maternal ophthalmic arteries and the average of four measurements of PSV Ratio were recorded.

Color flow imaging of left and right uterine arteries by transabdominal ultrasound and mean UtA-PI recorded. Cut off value of ophthalmic artery PSV ratio was taken as 0.60 and uterine artery PI was taken as 95th centile. The patients were classified as high risk or low risk based on the cut-off values of uterine and ophthalmic artery Doppler indices. Patients were followed up with monthly visits till 28 weeks, then every 2 weeks till 36 weeks and weekly thereafter till delivery. Antepartum complications were recorded and appropriate treatment instituted. When complications arose, women were seen more frequently. Interval growth scans were performed as required. Development of early onset pre-eclampsia (when the women develop features of pre-eclampsia before 34 weeks of gestation) or late onset pre-eclampsia (when the women developed features of pre-eclampsia at 34 weeks of gestation or beyond) was noted.

Delivery outcomes included gestational age at delivery, need and indication for induction of labour, mode of delivery, intrapartum and postpartum complications like eclampsia, HELLP, DIC, abruption or other neurological complications were noted. Neonatal outcomes such as birthweight, prematurity, fetal growth restriction, need for NICU admission, number of days of hospitalization and fetal demise were recorded. Data was recorded on a predesigned proforma.

***Statistical analysis***

The data on categorical variables was presented as n (% of subject) and the values on continuous variables was presented as Mean±Standard deviation (SD). The statistical significance of difference of distribution of categorical variables was tested using Chi-Square test or Fisher's exact probability test for 2×2 contingency table if more than 20% of cells have expected count less than 5.

Receiver operating characteristic curve (ROC) was used to obtain the optimal cut-off value. The diagnostic efficacy measures such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy will be calculated with appropriate reference standard or gold standard. P-values less than 0.05 was considered to be statistically significant. All hypotheses were formulated using two tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data was statistically analysed using Statistical Package for Social Sciences (SPSS ver 26.0, IBM Corporation; NY, USA) for MS Windows.

## RESULTS

We performed a prospective observational study to evaluate and compare the efficacy of ophthalmic artery doppler with uterine artery doppler in the prediction of preeclampsia. 127 registered antenatal cases, who delivered at this institute. The following observations were made during the study: The incidence of pre-eclampsia was 9.4%. Mean age of cases with PE was significantly more than cases without PE 35.8 vs 32.3 years. (p<0.01). (Figure 1)

No difference in BMI was seen among cases with and without PE (p-0.24). No association was observed between pre-eclampsia and gravidity (p-1.0). No association was observed between pre-eclampsia and mode of conception (p- 0.319).

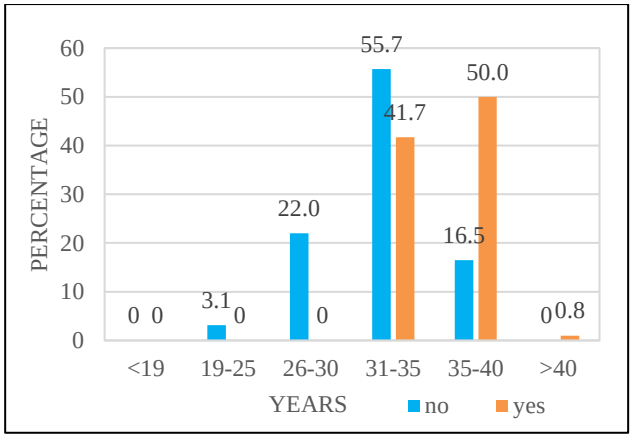


**Figure 1: Maternal age.**

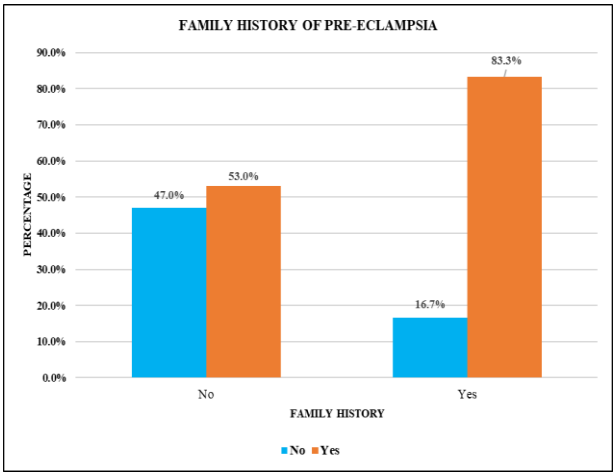


**Figure 2: Family history of pre-eclampsia.**

A significant association was observed between positive family history and PE (p<0.01) (Figure 2). 75% women developed early onset preeclampsia and 25% developed late onset pre-eclampsia (Table 1). Mean uterine artery pulsatility index was higher in PE cases as compared to cases without PE (1.91 vs 1.27; p-0.03). On ROC analysis, mean uterine artery pulsatility index was observed as a significant predictor for development of PE (AUC – 0.79; p<0.01), its sensitivity and specificity were 83.3% and 68.7% with accuracy of 76.0% (Table 2). Mean arterial pressure was significantly higher among cases of PE (108.94 vs 86.42 mm Hg; p<0.001). On ROC analysis, MAP was observed as a significant predictor for development of PE (AUC – 0.937; p<0.01). At a cut-off of 95.6 mm Hg, its sensitivity and specificity were 91.7% and 87.8% with accuracy of 89.8% (Table 3). On imaging the ophthalmic artery means PSV 2 values (27.54 vs 23.46; p<0.01) and PSV ratio (0.8 vs 0.61; p<0.01) were significantly higher among pre-eclampsia mothers (Table 4). On ROC analysis, ophthalmic artery parameters i.e. PSV2 and PSV ratio both were observed as significant predictors for development of PE (p<0.01), PSV2 had sensitivity 83.3% and specificity was 58.3% with accuracy of 70.8% and PSV Ratio has sensitivity of 83.3%, specificity of 61.7% with accuracy of 72.5% (Table 4). On ROC analysis, combined ophthalmic artery doppler parameters were observed as significant predictors for development of PE (AUC – 0.832; p<0.01) with a sensitivity and specificity of 58.3% and 90.4%, PPV of 38.9% and NPV of 95.4% with overall accuracy of 87.4% (Table 5).

On ROC analysis, combined uterine and ophthalmic artery doppler parameters were observed as significant predictors for development of PE (AUC – 0.896; p<0.01) with a sensitivity and specificity of 66.7% and 93.9% PPV of 53.3%, NPV of 96.4% with overall accuracy of 91.3% (Table 5). On ROC analysis, combined MAP, uterine and ophthalmic artery doppler parameters were observed as significant predictors for development of PE (AUC – 0.969; p<0.01) with a sensitivity and specificity of 91.7% and 98.3%, PPV of 84.6%, NPV of 99.1% with overall accuracy of 97.6% (Table 5).

Mean gestational age at the time of delivery was significantly lower in PE cases 35.91 vs 38.03 weeks(p<0.01). (Table 6). A significantly higher number of PE cases underwent LSCS (75% vs 64.3%; p<0.01) (Table 6). Overall prevalence of low birth weight was 14.2% in our study. Mean birth weight of babies delivered to pre-eclamptic mothers was significantly lower (2.56 vs 2.94 Kg; p-0.023). A significantly higher number of PE cases delivered low birth weight babies (41.7% vs 11.3%; p–0.014) (Table 7). NICU admission rate was significantly higher in babies delivered to PE mothers (41.7% vs 22.8%; p-0.014). There was one still birth (Table 8).

**Table 1: Gestational age at onset of pre-eclampsia.**

| Gestational age at development of PE (Weeks) | | Total, N (%) | |
|---|---|---|---|
| **Early onset** | <28 | 9 (75%) | 5 (41.7%) |
| | 28+1-34 | | 4 (33.3%) |
| **Late onset** | 34+1-36+6 | 3 (25%) | 2 (16.7%) |
| | 37-39+6 | | 1 (8.3%) |
| | >40 | | 0 (0%) |
| | **Total** | | 12 (100%) |

**Table 2: Uterine artery doppler PI.**

| Uterine artery PI | Pre-eclampsia | N | Mean | Sd | Min | Max | P value |
|---|---|---|---|---|---|---|---|
| | No | 115 | 1.27 | 0.5 | 0.6 | 2.56 | 0.03 |
| | Yes | 12 | 1.91 | 0.32 | 1.04 | 2.22 | |

| Test result variables | Area | SE | P value | Asymptotic 95% confidence interval | |
|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound |
| Uterine artery PI | 0.79 | 0.05 | <0.01 | 0.69 | 0.88 |

| Uterine artery PI | Sensitivity | Specificity | Accuracy |
|---|---|---|---|
| | 83.30% | 68.70% | 76% |

**Table 3: Mean arterial pressure.**

| MAP (mm Hg) | Pre-eclampsia | | Total, N (%) |
|---|---|---|---|
| | No n (%) | Yes n (%) | |
| <85 mmHg | 78 (67.8%) | 1 (8.3%) | 79 (62.2%) |
| >85 mmHg | 37 (32.1%) | 11 (91.7%) | 48 (37.8%) |
| Total | 115 (100%) | 12 (100%) | 127 (100%) |
| Mean | 86.2 | 108.9 | |
| SD | 7.3 | 10.9 | |
| P value <0.001 | | | |
| Area under the curve | | | |

| Test result variables | Area | SE | P value | Asymptomatic 95% confidence interval | |
|---|---|---|---|---|---|
| | | | | Lower bound | Upper bound |
| | 0.937 | 0.051 | <0.01 | 0.836 | 1 |

| MAP | Sensitivity | Specificity | Accuracy |
|---|---|---|---|
| | 91.70% | 87.80% | 89.80% |

**Figure 4: Mean ophthalmic artery doppler parameters and ROC analysis of individual ophthalmic artery doppler parameters for prediction of pre-eclampsia.**

| Ophthalmic artery doppler parameters (Mean) | Pre-eclampsia | N | Mean | SD | Min | Max | P value |
|---|---|---|---|---|---|---|---|
| PI | No | 115 | 1.86 | 0.42 | 0.9 | 3.41 | 0.27 |
| | Yes | 12 | 1.71 | 0.35 | 1.11 | 2.4 | |
| PSV1 | No | 115 | 39.05 | 9.77 | 17.26 | 68.6 | 0.338 |
| | Yes | 12 | 36.12 | 9.84 | 25.31 | 59.26 | |
| PSV2 | No | 115 | 23.46 | 6.68 | 8.27 | 42.82 | 0.007 |
| | Yes | 12 | 27.54 | 3.79 | 22.45 | 33.33 | |
| PSV ratio | No | 115 | 0.61 | 0.12 | 0.33 | 1.23 | 0.002 |
| | Yes | 12 | 0.8 | 0.17 | 0.49 | 1.02 | |
| Area under the curve | | | | | | | |

| Test result variables | Area | SE | P value | Asymptotic 95% confidence interval | |
|---|---|---|---|---|---|
| | | | | lower bound | upper bound |
| PSV2 | 0.71 | 0.06 | 0.02 | 0.6 | 0.82 |
| PSV ratio | 0.82 | 0.07 | <0.01 | 0.67 | 0.96 |

| Variables | Sensitivity | Specificity | Accuracy |
|---|---|---|---|
| PSV2 | 83.30% | 58.30% | 70.80% |
| PSV ratio | 83.30% | 61.70% | 72.50% |

*PSV1 values cannot be clubbed as they are not significant

**Table 5: ROC analysis.**

| Area under the curve (combined ophthalmic artery doppler) | | | | | |
|---|---|---|---|---|---|
| **Test result variables (PSV2;PSV ratio)** | **Area** | **SE** | **P value** | **Asymptotic 95% confidence interval** | |
| | | | | **Lower bound** | **Upper bound** |
| | 0.832 | 0.81 | <0.001 | 0.621 | 0.941 |
| | Sensitivity | Specificity | PPV | NPV | Accuracy |
| | 58.30% | 90.40% | 38.90% | 95.40% | 87.40% |
| **Area under the curve (ophthalmic artery + uterine artery doppler)** | | | | | |
| **Test result variable(s) - (PSV2; PSV ratio; UA-PI)** | **Area** | **SE** | **P value** | **Asymptotic 95% confidence interval** | |
| | | | | **Lower bound** | **Upper bound** |
| | 0.896 | 0.083 | <0.001 | 0.627 | 0.971 |
| | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Accuracy** |
| | 66.70% | 93.90% | 53.30% | 96.40% | 91.30% |
| **Area under the curve (ophthalmic artery +uterine artery doppler+ MAP)** | | | | | |
| **Test result variable(s) - (PSV2; PSV ratio; UA-PI, MAP)** | **Area** | **SE** | **P value** | **Asymptotic 95% confidence interval** | |
| | | | | **Lower bound** | **Upper bound** |
| | 0.969 | 0.013 | <0.01 | 0.73 | 1 |
| | **Sensitivity** | **Specificity** | **PPV** | **NPV** | **Accuracy** |
| | 91.70% | 98.30% | 84.60% | 99.10% | 97.60% |

**Table 6: Gestation age at delivery and Mode of delivery.**

| **Gestational age at delivery (weeks)** | **Pre-eclampsia** | | **Total, N (%)** |
|---|---|---|---|
| | **No** | **Yes** | |
| | **N (%)** | **N (%)** | |
| **<28** | 1 (0.87%) | 0 (0%) | 1 (0.79%) |
| **28+1-34** | 2 (1.74%) | 2 (1.57%) | 4 (3.14%) |
| **34+1-36+6** | 9 (7.82%) | 7 (58.3%) | 16 (12.6%) |
| **37-39+6** | 90 (78.3%) | 5 (41.7%) | 95 (74.8%) |
| **≥ 40** | 11 (9.6%) | 0 (0%) | 11 (8.7%) |
| **Mean** | 38.03 | 35.91 | |
| **SD** | 2.13 | 2.54 | |
| **Min** | 24 | 24 | |
| **Max** | 41 | 41 | |
| **Total** | 115 (100%) | 12 (100%) | 127 (100%) |
| **Mode of delivery** | **Pre-eclampsia** | | **Total, N (%)** |
| | No | Yes | |
| | N (%) | N (%) | |
| **Vaginal** | 41 (35.7%) | 3(25.0%) | 44 (34.6%) |
| **LSCS** | 74 (64.3%) | 9 (75%) | 83 (65.4%) |
| **Total** | 115 (100%) | 12 (10%) | 127 (100%) |
| **P value <0.01** | | | |

**Table 7: Birth weight.**

| **Birth weight (kg)** | | **Pre-eclampsia** | | **Total** | |
|---|---|---|---|---|---|
| | | **No, N (%)** | **Yes, N (%)** | **N (%)** | |
| **LBW** | **≤2** | 4 (3.5%) | 2 (16.7%) | 6 (4.7%) | **P value=0.014** |
| | **2.1-2.5** | 9 (7.8%) | 3 (25.0%) | 12 (9.4%) | |
| **2.6-3** | | 50 (43.4%) | 5 (41.7%) | 55 (43.3%) | |
| **3.1-3.5** | | 46 (40.0%) | 2 (16.7%) | 48 (37.7%) | |
| **3.6-4** | | 5 (4.3%) | 0 (0.0%) | 5 (3.9%) | |

| Birth weight (kg) | Pre-eclampsia | | Total |
|---|---|---|---|
| | No, N (%) | Yes, N (%) | N (%) |
| **>4** | 1 (0.9%) | 0 (0.0%) | 1 (0.8%) |
| **Total** | 115 (100%) | 12 (100%) | 127 (100%) |
| **Mean** | 2.94 | 2.56 | |
| **SD** | 0.54 | 0.67 | |
| **Min** | 0.24 | 1.20 | |
| **Max** | 4.36 | 3.20 | |
| **P value - 0.023** | | | |

**Table 8: NICU admission.**

| NICU admission | Pre-eclampsia | | Total |
|---|---|---|---|
| | No | Yes | N (%) |
| | N (%) | N (%) | |
| **No** | 87 (76.3%) | 7 (58.3%) | 94 (74.01%) |
| **Yes** | 26 (22.8%) | 5 (41.7%) | 32 (25.1%) |
| **Total** | 114 (100%) | 12 (100%) | 126 (99.2%) |
| **P value - 0.014** | | | |

## DISCUSSION

Doppler imaging is a non-invasive technique that assesses feto-placental circulation without interfering with a woman's pregnancy.6 It has been demonstrated that parameters like high resistance index, pulsatility index, and persistent uterine artery notching in the uterine artery Doppler wave form have good screening efficacy for prediction of PE.[7] A number of peripheral arterial Doppler indices, including ophthalmic artery Doppler, have been studied as possible indicators of the onset of PE in addition to uterine artery Doppler.

The current study aimed to evaluate the effectiveness of ophthalmic artery doppler velocimetry with uterine artery doppler and test its predictive value regarding the occurrence of pre-eclampsia. We included 127 women who had booked and delivered in our hospital. An obstetric ultrasound scan with ophthalmic and uterine artery doppler was performed between 19-23 weeks of gestation.

### *Incidence of pre-eclampsia*

The incidence of pre-eclampsia in the present study was 9.4%. Pre-eclampsia occurs in 5–8% of pregnancies worldwide.[8] Mehta B et al, in a hospital-based study observed a total of 931 pregnant women. The prevalence of hypertension in pregnancy was found to be 6.9%.[9] Hypertensive disorders of pregnancy were reported to be 7.49% and 8.96%, respectively, in other hospital-based studies in India.[10,11]

### *Maternal age*

In the present study, mean age of cases with PE was significantly higher than cases without PE (35.83 vs 32.27 years; p<0.01).

In a study by Nadkarni et al. majority of women were in the age group of 31-35 years.10 In another similar study by Kheir et al. most of the women affected by hypertensive disorders of pregnancy were aged 21-30 years (mean age 26.2 years).[12] Hak J et al, observed the mean age in controls and in women with HDP as 25.17 and 25.75 years respectively. (p>0.05).[13]

### *BMI*

In the present study mean BMI of cases with pre-eclampsia was 30.9 and without pre-eclampsia was 29.0. No difference in BMI was seen among cases with and without PE (p-0.24).

Yawen Shao et al. reported that compared to women with normal pre-pregnancy BMI, those who were overweight/obese had an increased risk of pre-eclampsia (OR = 1.81; 95%CI: 1.37–2.39). No association was found for early-onset pre-eclampsia.[14]

### *Gravidity*

In the present study, out of 127 women 56.7% were primigravida and 43.3% were multigravida. Out of 12 cases who developed pre-eclampsia, 58.3% were primigravida and 41.7% were multigravida. No association was observed between pre-eclampsia and gravidity (p-1.0) .

In a study by O'Gormon N out of 58884 women 49.4% were primigravida and 50.6% were multigravida.[15] Owiredu et al studied the risk factors for pre-eclampsia in 100 pregnant women in Ghana and did not find any association between gravidity and pre-eclampsia.[16]

***Family history of pre-eclampsia***

In the present study out of 127 women, 71 had family history of pre-eclampsia, out of which 10 women developed pre-eclampsia. We observed a significant association between positive family history and PE ($p<0.01$). Family history of hypertension is a risk factor because families share environmental or behavioural exposures that may underlie pre-eclampsia risk. Family history of pre-eclampsia quadruples the risk.[17] Owiredu et al, stated that women with a family history of hypertension were about 7 times at risk of developing PIH as compared to women without family history of hypertension.[16]

***Mode of conception***

In the present study of 127 women 85.8% conceived naturally and 14.2% conceived with help of ovulation induction drugs and IVF. No association was found between mode of conception and development of PE.

On the other hand, Uri P Dior et al, found pre-eclampsia complicated 3 out of 270 (1.1%) natural conception pregnancies and 17 out of 135 (12.6%) oocyte donation conceptions. After adjusting for confounders, oocyte donation pregnancies were found to be associated with a 12-fold increased risk for pre-eclampsia ($P = 0.001$).[18]

***Gestational age at onset of pre-eclampsia***

Out of 127 women in our study, 12 women developed pre-eclampsia and out of 12 women who developed pre-eclampsia 75% developed early onset PE at <34 weeks of gestation and 25% developed late onset PE at >34 weeks of gestation. Lisonkova S et al in a study of 456,668 deliveries in Washington State, during 2003-2008 found overall pre-eclampsia rate of 3.1% with early and late onset pre-eclampsia rates of 0.38% and 2.72%, respectively.[19]

***Role of uterine artery doppler***

Mean uterine artery pulsality index (UtA-PI) was significantly higher in PE cases as compared to cases without PE (1.91 vs 1.27; p-0.03). On ROC analysis, uterine artery PI was observed as a significant predictor for development of PE ($p<0.01$). Mean uterine artery pulsality index (UA-PI) has sensitivity and specificity of 83.3% and 68.7% with overall efficacy of 76% for detection of pre-eclampsia. Neravi A et al observed mean PI as 0.89 at 12-16 weeks and 0.64 at 24-26 weeks. In pre-eclampsia mean PI at 12-16 weeks was 0.9573 and at 24-26 weeks was 0.7968, which was statistically significant as compared to non-preeclamptic group ($p<0.01$).[20]

***Role of mean arterial pressure (MAP)***

In our study, we found that 79 women had MAP<85 mmHg and the remaining 48 women had MAP of >89.5mmHg. Out of the 79 women with low MAP, one woman (8.3%) developed pre- eclampsia and other 78 women did not have PE. Out of the 48 women with high MAP, 11 of them (91.7%) developed pre-eclampsia and remaining 37 women (32.1%) did not have PE. Mean arterial pressure was significantly higher among cases of PE (108.94 vs 86.42 mm Hg; $p<0.01$). On ROC analysis, MAP was observed as a significant predictor for development of PE (AUC – 0.737; $p<0.01$). Its sensitivity and specificity were 91.7% and 87.8% with accuracy of 89.8%.

Out of 9149 women with singleton pregnancies in a study by Poon et al, 8061 cases were unaffected by PE or GH, 37 developed PE requiring delivery before 34 weeks, 128 had late-PE, and 140 had GH. The systolic BP, diastolic BP, and MAP were significantly higher in early-PE, late-PE, and GH than in the controls ($p<0.0001$). The systolic BP was significantly higher in early-PE than in late-PE ($p=0.008$) and both systolic BP and MAP were significantly higher in early-PE than in GH ($p<0.01$). The best performance in screening was provided by MAP. The median of MAP in various groups of unaffected, early PE, late PE and gestational hypertension was 84.3, 94.5, 93.8 and 92.4mm Hg respectively.[21]

***Role of ophthalmic artery doppler***

Due to their morphological, physiological, and embryological similarities, the ocular circulation depicts the state of the hemodynamic cerebral flow, and Doppler examinations of the ocular arteries have been used to manage conditions that damage the cerebral vasculature.[22]

Thus, in the context of gestational hypertension, cerebral overflow seen by ophthalmic artery Doppler ultrasound may indicate a possible danger of cerebral complications. Furthermore, it is recognised that the ophthalmic artery serves as the only investigative tool in Doppler because Doppler readings from other, bigger intracranial vessels, such as the middle cerebral artery, do not indicate preeclamptic alterations.[23] In the present study, we recorded ophthalmic artery doppler parameters including peak systolic velocities (PSV) 1 and 2 of both eyes, pulsatility index, PSV Ratio at 19-23 weeks and cases were followed up after that to look for the development of PE. Mean PSV2 values (27.54 vs 23.46, $p<0.01$) and PSV ratio (0.8 vs 0.61, $p<0.01$) were significantly higher among pre-eclampsia mothers. On ROC analysis, ophthalmic artery parameters i.e. PSV2 and PSV ratio were observed as significant predictors for development of PE ($p<0.01$). PSV2 had a sensitivity and specificity of 83.3% and 58.3% with overall efficacy of 70.8% while for PSV ratio the sensitivity and specificity were 83.3% and 61.7% with overall efficacy of 72.5% respectively for detection of pre-eclampsia. Overall, for prediction of PE, ophthalmic artery doppler had a sensitivity and specificity of 58.3% and 90.4% with overall accuracy of 87.4%.

Doppler analysis of the ophthalmic artery in pregnant women was first proposed by Hata T et al, in 1992. Peak

systolic velocities (PV) were calculated and observed to be significantly higher in the PE group. Hata T et al, in another study in 1995, observed that peak systolic velocity (49.0+/-11.8 (SD) cm/s) in mild pre-eclampsia was significantly higher (p<0.0001) than that (32.1+/-9.5 cm/s) in normotensive pregnant women.[24]

de Oliveira CA et al, observed significant differences between PSV ratio in women with severe pre-eclampsia compared to the other groups.[25] The optimal cutoff value for PSV ratio as determined by the receiver operating characteristic curves was >0.784 as compared to >0.62 as observed in our study.

Kalafat E et al, did a meta-analysis to determine the accuracy of ophthalmic artery Doppler in pregnancy for the prediction of pre-eclampsia (PE).[5] Peak ratio above 0.65 showed a good diagnostic accuracy with an AUC of 0.67 (95% CI, 0.58–0.77) for early-onset PE and 0.57 (95% CI, 0.51–0.63) for late-onset disease.

***Role of combined ophthalmic artery doppler and uterine artery doppler and mean arterial pressure***

On analysing the efficacy of combined uterine and ophthalmic artery doppler parameters, we observed a sensitivity and specificity of 66.7% and 93.9% with overall accuracy of 91.3% (AUC–0.896, p<0.01). On ROC analysis, combined MAP, uterine and ophthalmic artery doppler parameters were observed as significant predictors for development of PE (AUC–0.969, p<0.01). On including mean arterial pressure, the overall accuracy increased to 97.6% with sensitivity and specificity of 91.7% and 98.3% (AUC–0.969, p<0.01).

Matias DS et al, observed that performance of ophthalmic artery doppler was similar to that of uterine artery doppler for predicting PE. Additionally, the AUC increased significantly from 0.82 to 0.88 when it was incorporated into the model containing clinical variables and Uterine Doppler indices.[26] Contrary to this, Sarno M et al, observed that ophthalmic artery indices did not improve the prediction of PE provided by maternal factors alone.[27]

***Gestational age at delivery***

Mean gestational age at time of delivery was significantly lower in PE cases (35.91 vs 38.03 weeks; p<0.01). A significantly higher number of PE cases delivered pre-term (41.7% vs 13.9%; p<0.01). In a study by Rosnanh Sultan et al, of 40212 women, those with pre-eclampsia had a higher risk of preterm delivery (67.7%).[28]

***Mode of delivery***

In the present study, a significantly higher number of PE cases underwent LSCS (75% vs 64.3%; p<0.01). This is similar to what other authors have observed.

In a study by Nadkarni et al. the rate of Caesarean section was 55% within the PE group as compared to 29% in controls.[10]

***Neonatal outcome***

*Birth weight*

Overall prevalence of low birth weight was 14.2% in present study. A significantly higher number of PE cases delivered low birth weight babies (41.7% vs 11.3%; p–0.014). Mean birth weight of babies delivered to pre-eclamptic mothers was significantly lower (2.56 vs 2.94 Kg; p-0.023). Significantly higher number of women with pre-eclampsia delivered low birth weight babies (41.7% vs 11.3%; p–0.014).

A multicentric prospective study of 30639 women with singleton pregnancies showed that the prevalence of SGA with PE was 82%, 47% and 30% in those delivered at <34 weeks, between 34-37 weeks and ≥37 weeks respectively. the frequency of SGA in pregnancies without PE was 44%, 21% and 8% respectively.[29]

*NICU admission*

In the present study, out of 127 neonates, one was still born and 25.1% babies required NICU admission. NICU admission rate was significantly higher in babies delivered to PE mothers (41.7% vs 22.8%; p-0.014). Our findings are in accordance with previous studies which observed that pregnancies complicated by hypertension are characterized by an increased rate of preterm delivery and NICU admissions as compared with normal pregnancies. In a study by Ferrazini et al, the rate of early pre-term delivery (<32weeks) was 21.2% in PE and 7% in controls.[30]

It being a single centres study may limit the generalizability of the findings to other settings or populations. Although the study included 127 patients, the relatively small sample size might limit the statistical power and the ability to detect associations with less common risk factors. Larger studies are required to confirm the findings and identify additional predictors of PE. The study population may lack diversity in terms of socioeconomic status, ethnicity, and other demographic factors, which could influence the generalizability of the findings. Future research should include more diverse populations to ensure the findings are applicable to a broader audience. The study did not follow participants beyond delivery to assess long-term maternal and neonatal outcomes. Longitudinal studies are necessary to understand the long-term impacts of PE and the effectiveness of early detection and management.

## CONCLUSION

Ophthalmic artery Doppler is a simple, accurate and objective technique with a standalone predictive value for

the development of early-onset PE better than that of uterine artery Doppler evaluation. The association between ocular Doppler indices and PE may be due to the mother's hemodynamic adjustment during pregnancy rather than being a result of trophoblast invasion

Ophthalmic artery parameters i.e. PSV2 and PSV ratio were observed as significant predictors for development of PE. The predictive accuracy of doppler assessment for prediction of pre-eclampsia increases with the inclusion of uterine artery doppler and ophthalmic artery doppler readings for assessment. Combined MAP, uterine and ophthalmic artery doppler parameters were observed as significant predictors for development of PE with a higher sensitivity, specificity and overall accuracy.

The findings of this study justify efforts to define the effectiveness and underlying mechanism whereby two seemingly unrelated maternal vessels can be used for the prediction of a disease considered a 'placental disorder'.

Uterine and ophthalmic artery doppler may be included in hospitals with facilities to identify group of patients at risk of developing pre-eclampsia. This will help to monitor them closely and manage effectively so as to reduce maternal and neonatal morbidity.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Adlakha E, Khanijo V, Unni J, Bapat A, Thakar S. Predictive value of ophthalmic artery doppler in pre-eclampsia development. Int J Reprod Contracept Obstet Gynecol 2024;13:3691-701.