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Research Article

# Ophthalmic Artery Doppler in Combination with N-Terminal Prohormone of Brain Natriuretic Peptide in Prediction of Pre-Eclampsia at 28-32 Weeks Gestation

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**Abstract**

**Introduction:** This study aimed to assess ophthalmic artery Doppler in combination with N-terminal prohormone of Brain Natriuretic Peptide in the prediction of pre-eclampsia (PE) at 28-32 weeks' gestation.

**Methods :**This is a prospective study on singleton pregnant women who were referred to Imam Khomeini Hospital for routine pregnancy care at the gestational age of 28 to 32 weeks from June 2023 to June 2024. The mother's demographic information, medical history, bilateral ophthalmic artery Doppler, and NT-proBNP levels were recorded. Area under the curve (AUC) and logistic regression models were used to analyze the data.

**Resuls :** One hundred sixty pregnant women with a gestational age of 28-32 weeks were included, and 36 (22.5%) of them developed PE. The averages of PSV ratio in the PE pregnancies were 0.60±0.12, and in the normal pregnancies were 0.75±0.09. The average PSV ratio in the PE pregnancies was significantly higher than in normal pregnancies (P< 0.001). Also, the average PSV2 in PE pregnancies was significantly higher than in normal pregnancies (P < 0.015). The frequency of fetus death was higher in the PE pregnancies (P = 0.041). The ROC curve for PSV ratio in the prediction of PE showed that 0.69 was the best cut-off value of PR (sensitivity 0.83; specificity 0.81). The regression model for the development of PE revealed a significant association only with the PSV ratio (p = 0.016).

**Conclusion:** At 28–32 weeks of pregnancy, the ophthalmic artery PSV ratio was found to be helpful in predicting future PE development, especially preterm PE. It could be valid on its own or in combination with other biomarkers. The mean of NT-proBNP in PE pregnancies was higher than in normal pregnancies. However, the differences were insignificant, and this insignificant difference in this study may be related to differences in the evaluation of participants during gestation weeks and differences in population samples between studies. More studies are needed to assess this biomarker in combination with ophthalmic artery Doppler to predict PE.

**Keywords:** Pre-eclampsia, Ophthalmic artery Doppler, N-Terminal Prohormone of Brain Natriuretic Peptide.

## Introduction

Pregnancy hypertension, including PE, causes complications in 6 to 8% of pregnancies worldwide and is considered a cause of maternal morbidity and mortality. Timely diagnosis of high-risk pregnancy allows us to reduce morbidity and mortality in both mother and fetus groups with treatment strategies [1-4]. Neurological and cerebral complications, including eclampsia and intracranial bleeding, are among the

most essential maternal problems following hypertension [5]. Blood pressure disorders are responsible for 18% of maternal deaths worldwide, with an estimated 62,000 to 77,000 deaths per year [1]. Blood pressure disorders are classified into four types: 1-chronic hypertension, 2-pregnancy hypertension, 3-preeclampsia and preeclampsia added to chronic hypertension, and 4-white coat hypertension [2]. Given the high morbidity and mortality of this disease, PE risk assessment should be considered in every trimester of pregnancy. Although there is no way to prevent PE after PE screening in the second and third trimesters, it can identify the high-risk group in order to closely monitor and reduce adverse pregnancy complications, as well as provide the right time and place for delivery for those who are exposed to PE [6–9]. Recently, several studies that used the ophthalmic artery Doppler to show cerebral hemodynamic flow found that it can be used to predict cerebral perfusion in PE [10–14].

On the other hand, in preeclampsia patients, a serum marker called NT-proBNP is released into the bloodstream in response to increased heart wall stretching. In preeclampsia, eclampsia, and HELLP patients, NT-proBNP increases in response to increased left ventricular filling pressure and subclinical left ventricular diastolic dysfunction [15–18].

The ophthalmic artery, which has anatomical and functional similarities with the intracranial vasculature, is an easily accessible vessel for Doppler assessment that provides information on the less accessible intracranial circulation. Extensive evidence indicates that, in pregnancies with PE, compared to normal pregnancies, there is a reduction in impedance to flow and an increase in flow velocity in the ophthalmic arteries [19-22].

Because ophthalmic artery Doppler measurement can be used as an ultrasound marker and NT-proBNP can be used as a laboratory marker, finding patients at risk of preeclampsia early is very important. These two things can be used together to make finding people at risk of PE easier. This study aimed to investigate the synergistic effect of these two factors in predicting preeclampsia in pregnant women between the ages of 28 and 32. Additionally, the study aims to gather pregnancy outcomes, such as the following, from the study group and analyze the correlation between these outcomes, the NT-proBNP level, and ophthalmic artery Doppler parameters.

## Methods

This is a prospective study on singleton pregnant women who were referred to Imam Khomeini Hospital for routine pregnancy care at the gestational age of 28 to 32 weeks from June 2023 to June 2024. Pregnancies diagnosed with aneuploidy and significant fetal anomalies, as well as women with preeclampsia, multiple pregnancies, people with heart diseases, cerebrovascular and eye diseases, rheumatological diseases, and people with chronic hypertension and diabetes, were excluded. The mother's demographic information, medical history, bilateral ophthalmic artery Doppler, and NT-proBNP levels were recorded. Two ccs of venous blood samples were taken from patients who did not need to fast; all samples were measured in a laboratory, and the ECLA laboratory method was used to check the NT-proBNP level in blood samples. A linear 6–12 MHz probe was used to obtain the Doppler of the ophthalmic artery. The patient lies supine with closed eyes, and the probe is placed on the upper eyelid, which is moved craniocaudally without pressure. The ophthalmic artery can be seen 15 mm from the optic disc towards the inside of the optic nerve. The insonation angle is less than 20 degrees (2 mm), and the depth is 3–4.5 cm. The ophthalmic artery Doppler is taken from the right eye, then the left eye, and then again from the right eye to the left eye. We record the average of the first peak of systolic velocity, the second peak of systolic velocity, and the ratio of the second to the first peak of systolic velocity. The following items include an analysis of the Doppler direction of the four pulsatility indexes.

For the standard 28–32-week scan, the subject was in the supine position. After applying conduction gel, a 7.5-MHz linear transducer was softly and transversely positioned over her closed upper eyelid to complete this procedure. After that, three to five comparable waveforms were recorded using a pulsed-wave Doppler; the parameters were as follows: the depth was 3.0-4.5 cm, the sample gate was 2 mm, the high-pass filter was set to 50 Hz, and the pulse repetition frequency was set to 125 kHz. The angle of insonation was maintained at less than 20°. A sonographer performed the ultrasound scans for all patients, and little training was required to see the ocular arteries, capture flow velocity waveforms, and record the relevant indices in all of the patients without experiencing any technical issues. The first and second systolic velocity peaks, PI, and the ratio of the

second to first systolic velocity peak (PSV ratio) were the four indices that were analyzed. The machine automatically determined the first systolic velocity peak and PI, measured the second systolic velocity peak by hand and computed the PSV ratio.

All patients received an informed consent form. The ethical committee of Tehran University of Medical Science approved the protocol of this study.

SPSS-26 was used to analyze the data. Chi-2 and Fisher's exact tests were used to determine the relationship between qualitative variables. The T-test and Mann-Whitney U-test were used to compare the mean of variables between the groups. A logistic regression model was used to evaluate the relationship between variables and predictions. Areas under the receiver-operating-characteristics curve (AUC) were used to detect a cut-off point for predicting PE. A P-value less than 0.05 was considered statistically significant.

## Results

Overall, 160 pregnant women with a gestational age of 28-32 weeks were included, and 36 (22.5%) of them developed PE. Maternal, pregnancy characteristics, ophthalmic artery Doppler marker, and NT-proBNP of the study population are presented in Table 1. The average age in the PE group was 35.33±5.31, and in the normal group was 32.14±5.88 years. The mean age in the PE cases was higher than in normal cases (P = 0.037). There were no differences between the PE and normal pregnancies regarding weight, PSV1, PI, RI, and NT-proBNP (P>0.05) (Table 1).

The averages of PSV ratio in the PE group were 0.60±0.12, and in the normal group were 0.75±0.09. The average PSV ratio in PE pregnancies was significantly higher than in normal pregnancies (P < 0.001). Also, the average PSV2 in PE pregnancies was significantly higher than in normal pregnancies (P < 0.015).

The PE group's gestational age was significantly lower (P < 0.001). Also, birth weight was significantly lower in the PE group (P < 0.001) (Table 1).

Adverse maternal outcomes such as fetus death and NICU admission were presented in Table 1. The frequency of fetus death was higher in the PE group (P = 0.041) (Table 1).

ROC curve for PSV ratio in the prediction of PE showed an area under the curve [AUC] of 0.841 | (95%CI 0.747–0.935) (Fig. 1), and the Youden index (J) pointed out 0.69 as the best cut-off value of PR (sensitivity 0.83; specificity 0.81) as an index of disease severity in the present study. The regression model for the development of PE revealed a significant association only with the PSV ratio (p = 0.016). Maternal OA Doppler PR value and NtproBNP were not associated with PE (P > 0.05 (Table 2).

Table 1: Comparing variables between the PE and normal pregnancies

| Items | Normal | PE | P-value |
|---|---|---|---|
| **Age (years)** | 32.14±5.88 | 35.33±5.31 | 0.037 |
| **Weight (Kg)** | 79.41±12.42 | 77.38±7.27 | 0.572 |
| **Gestational age (weeks)** | 36.20±2.42 | 33.00±3.78 | <0.001 |
| **Birth weight (g)** | 2852.74±536.80 | 1779.16±647.97 | <0.001 |
| **PSV1** | 38.96±11.58 | 41.67±13.48 | 0.489 |
| **PSV2** | 24.67±9.33 | 31.66±11.47 | 0.015 |
| **PSV ratio** | 0.60±0.12 | 0.75±0.09 | <0.001 |
| **PI** | 0.60±0.15 | 0.52±0.14 | 0.094 |
| **RI** | 0.46±0.09 | 0.44±0.10 | 0.335 |
| **NT-proBNP** | 50.27±68.49 | 91.52±139.67 | 0.271 |
| **Fetus death** | 0 | 4 (11.1%) | 0.041 |
| **NICU admission** | 34 (27.4%) | 16 (44.4%) | 0.173 |

Table 2: Logistic regression model.

| Items | | B | S.E. | P-value | Exp (B) | 95.0% C.I.for EXP(B) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Model | Age | 0.068 | 0.071 | 0.336 | 1.071 | 0.932 | 1.230 |
| | Weight | -0.023 | 0.040 | 0.573 | 0.977 | 0.903 | 1.058 |
| | PSV1 | 0.060 | 0.117 | 0.607 | 1.062 | 0.845 | 1.334 |
| | PSV2 | -0.028 | 0.161 | 0.863 | 0.973 | 0.709 | 1.335 |
| | PSV Ratio | 19.271 | 8.140 | 0.018 | 2.340E8 | 27.594 | 1.985E15 |
| | PI | 7.498 | 6.159 | 0.223 | 1.805E3 | .010 | 3.157E8 |
| | RI | -0.618 | 7.743 | 0.936 | 0.539 | .000 | 2.101E6 |
| | Nt-proBNP | 0.004 | 0.005 | 0.417 | 1.004 | .995 | 1.013 |
| | Constant | -20.725 | 8.122 | 0.010 | 0.000 | | |

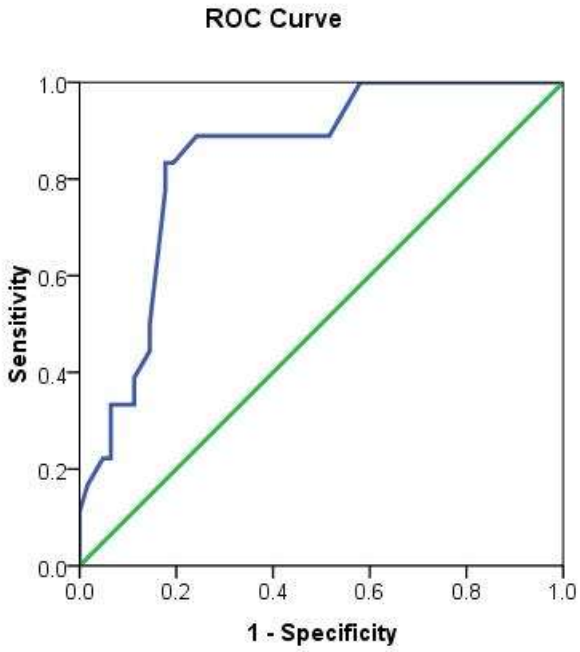


Figure1: ROC curve for Doppler peak ratio as a predictor of PE, Area=0.841

## Discussion

The ophthalmic artery Doppler may be a helpful biomarker for future PE pregnancies, particularly preterm PE with delivery at or before 37 weeks, according to this study of singleton pregnancies between 28 and 32 weeks. We assessed into the first, second, PSV ratio, and PI indices of systolic and diastolic velocity. First, we discovered that there was a considerable increase in the PSV ratio in PE pregnancies. The first peak of systolic velocity and PI were not significantly affected by PE; second, the second peak of systolic velocity was increased in PE

pregnancies, but the effect did not depend on gestational age at delivery; and third, the deviation from normal was more significant for early PE than for late PE.

Changes in the mother's cardiovascular system during pregnancy, like a rise in cardiac output and peripheral vascular resistance, happen before she shows any signs of PE. Thus, it should come as no surprise that changes in cerebral circulation occur prior to the onset of PE, as evidenced by the variations in the waveforms acquired from the ocular arteries.

Women who already have PE have quicker blood flow in their ocular arteries, according to several earlier studies. These results are consistent with our discovery that pregnant women who subsequently develop PE have a high second peak of systolic velocity. These investigations of established PE, however, also revealed decreased PI in addition to higher velocities. In contrast, in our study, women who developed PE did not experience any changes in PI [22-24]. The present study showed that the PSV ratio is the most reliable ophthalmic artery marker for PE prediction.

The possible utility of ocular artery Doppler in the second trimester of pregnancy for screening against the development of PE later on was investigated in two earlier investigations. Both investigations included high-risk pregnancies, and only the right ophthalmic artery was examined. In the first research, 347 fetuses were evaluated between 20 and 28 weeks of gestation, 40 of which (11.5%) resulted in PE. According to the authors, pregnancies that developed PE had more excellent PSV ratios and first and second peaks of systolic velocity than pregnancies that were not impacted. The second peak of systolic velocity had a 70% DR for PE and a 25% FPR as a screening tool, indicating the most significant difference between the groups. In the second study, 372 pregnancies were assessed between 18 and 23 weeks of gestation, of which 40 (10.8%) developed PE. The second peak of systolic velocity, PSV ratio, and PI did not significantly differ between the pregnancies that had PE and the unaffected pregnancies, according to the investigators [23, 24].

Sapantzoglou et al. (2020) discovered that the ophthalmic artery PSV ratio may be helpful in anticipating the onset of PE, particularly preterm PE, at 19–23 weeks of pregnancy [9]. This is true whether other biomarkers are added or taken alone.

According to Sarno et al. (2020), a subsequent birth with PE can be predicted based on the ophthalmic artery PSV ratio at 35–37 weeks' gestation, primarily if the delivery happens three weeks after the examination [25]. Additionally, cross-sectional investigations revealed that women with PE have higher ocular artery flow velocity and a lower flow-to-impedance when compared to normal pregnancies [15–16].

In a comprehensive study and meta-analysis, Melo et al. (2022) assessed the precision of various ocular artery Doppler measures in the supplementary diagnosis of preeclampsia. They showed that the ocular artery Doppler is an additional method that can find severe and high-risk preeclampsia with the highest sensitivity and specificity when PR and P2 parameters are used [26].

Chaves et al. (2017) found that maternal OA Doppler, which measures the ratio of velocity peaks $\geq 0.99$ in preeclampsia, may help find women who are more likely to have bad outcomes during pregnancy and pregnancies that are most likely to end early [27]. The present study showed that the frequency of fetus death was higher in the PE group, and the PE group had a higher PSV ratio than normal pregnancies.

In a 2013 systematic review of 12 studies, it was found that the NT-proBNP level does not change during pregnancy in healthy pregnant mothers. In contrast, in women with preeclampsia, the level of this hormone increases in the third trimester and remains high until 3-6 months after delivery [29]. Thanh and his colleagues published an article in 2021 showing that NT-proBNP increases significantly in preeclamptic patients [30]. In the present study, regardless of the significance, the mean of NT-proBNP in PE pregnancies was higher than in normal pregnancies, and this insignificant difference may be related to differences in gestation weeks' evaluation of participants and differences of population samples between studies.

## Conclusion

At 28–32 weeks of pregnancy, the ophthalmic artery PSV ratio was found to be useful for predicting future PE development, especially preterm PE. It could be useful on its own or in combination with other biomarkers. The mean of NT-proBNP in PE pregnancies was higher than in normal pregnancies. However, the differences were insignificant and this insignificant difference in this study may be related to differences in gestation weeks' evaluation of participants and differences of population samples

between studies. More studies are needed to assess this biomarker in combination with ophthalmic artery Doppler to predict PE.

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## Conflict of Interest Disclosures

We declare that there is no conflict of interest.

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None.

## Authors' Contributions

Concepts, data gathering, analyzing, writing and editing: Zahra Panahi, Zeinab Shabani, Fatemeh Shabani, Sedigheh Bourna, Sedigheh Hantoushzadeh, Fahimeh Ghotbizadeh Vahdani, and Razieh Akbari.

## Ethical Statement

The protocol of this study was approved in ethical committee of Tehran University of Medical Science with IR.TUMS.IKHC.REC.1402.232 code.

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