DOI: 10.7860/JCDR/2025/81194.21414

Original Article

Obstetrics and Gynaecology Section

Role of Uterine and Ophthalmic Artery Doppler Velocimetry in Second Trimester for Prediction of Preeclampsia in High-risk Pregnant Women: A Prospective Cohort Study

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ABSTRACT

Introduction: Preeclampsia is one of the major complications of pregnancy, with an incidence of 1-35% worldwide. There is currently no reliable screening test to predict adverse complications of preeclampsia. In the non gravid uterus and early gravid uterus, uterine spiral vessels have high-resistance blood flow, which changes to low resistance during a normal pregnancy. However, this phenomenon fails to occur in preeclampsia, resulting in high flow impedance.

Aim: To determine the occurrence of preeclampsia in high-risk pregnant women during the second trimester using the Pulsatility Index (PI) of the uterine and ophthalmic arteries.

Materials and Methods: A prospective cohort study was conducted at the tertiary care centre (TRIHMS) in Arunachal Pradesh within the Department of Obstetrics and Gynaecology from November 2022 to October 2024. Patients (n=100) in the second trimester of pregnancy, who had risk factors for developing preeclampsia, were enrolled in the study. The PI of the uterine artery and ophthalmic artery was obtained using a curvilinear and linear probe, respectively. Patients were then followed-up for the development of preeclampsia from the time of enrollment in the study until discharge from the hospital after delivery of the baby. Statistical analyses were performed using the Chi-square test, Student's t-test and Analysis of Variance (ANOVA).

Results: The age of participants ranged from 18 to 44 years, with a mean age of 26±5.01 years. The mean±SD of participants' weight, height, and Body Mass Index (BMI) were 66.37±7.99 Kg, 152.5±4.72 centimeters, and 28.48±6.35 kg/m^2, respectively. A total of 27 participants developed preeclampsia during the course of this study. The sensitivity of the uterine artery PI was found to be 25% and specificity was 87% at a cut-off value of ≥1.45. The ophthalmic artery PI had a sensitivity of 85% and specificity of 58% at a cut-off value of <1.76. The current study summarised that the ophthalmic artery Doppler has a higher Negative Predictive Value (NPV) (91%), while the uterine artery Doppler has higher specificity (87%) in detecting preeclampsia.

Conclusion: Doppler flow velocimetry is a non invasive and less time-consuming method of screening high-risk pregnancies, which can be made widely available. In cases where this screening test yields abnormal results in the second trimester, increased surveillance, timely follow-up and delivery in a well-equipped centre are essential to prevent or resolve maternal and foetal complications.

Keywords: Doppler flow velocimetry, Pregnancy, Pulsatiliity index

INTRODUCTION

Preeclampsia is a pregnancy-specific condition that occurs in women who were previously normotensive and develop hypertension (BP ≥140/90 mmHg) after the 20th week of pregnancy, recorded 4-6 hours apart, along with associated proteinuria of ≥300 mg/24 hours or end-organ damage [1]. According to the American Society of Obstetricians and Gynecologists (ACOG), preeclampsia is classified as non severe or severe. A BP of 140-160/90-110 mmHg is considered non severe preeclampsia, while the severe variety occurs when the patient presents with BP≥160/110 mmHg or exhibits any symptoms of end-organ damage such as thrombocytopenia, renal failure, hepatic necrosis, disruptions to the central nervous system and pulmonary oedema, even if BP is <160/110 mmHg [1,2].

The incidence of cases ranges from 1-35% worldwide [3], with 5-20% developing life-threatening or fatal complications, especially in those who develop preeclampsia during the early trimester of pregnancy [4,5]. The primary cause of preeclampsia is abnormal uteroplacental circulation due to the failure of the second wave of trophoblastic invasion into spiral arterioles. The high-resistance blood flow of spiral vessels in a non pregnant or early pregnant uterus typically becomes low-resistance flow during the normal physiological changes of pregnancy. However, this change does not occur in women destined to develop preeclampsia in the future, resulting in high impedance circulation. The resistance produced in this circulation is manifested as increased impedance in either or both uterine artery Doppler velocimetry waveforms [6], making it a non invasive screening tool for detecting changes in uterine arteries during pregnancy [7] by evaluating the Pulsatility Index (PI), Resistance Index (RI) and the presence of diastolic notching [8].

Lopez-Mendez MA et al., and Shahid N et al., in their studies, found that Doppler velocity waveform analysis of the uterine artery using color Doppler has high sensitivity and specificity in detecting pregnancy-induced hypertension and preeclampsia [9,10]. Doppler studies of the ocular vessels have also been utilised to assess, treat, and manage conditions affecting the cerebral vasculature, such as preeclampsia [11], because the ocular circulation mirrors the state of the haemodynamic cerebral circulation and because there are embryological, anatomical and functional similarities. Preeclamptic pregnant women exhibited lower impedance to flow and faster flow velocity waveforms from the ophthalmic arteries compared to normotensive pregnant women [12].

So far, there is no reliable screening test for predicting adverse complications, despite significant advancements in medical research, particularly in low-resource settings where high-end biochemical markers are unavailable. Hence, the present study was conducted to

analyse the role of uterine and ophthalmic artery Doppler velocimetry in the second trimester for the prediction of preeclampsia using PI.

MATERIALS AND METHODS

A prospective cohort study was conducted in the Department of Obstetrics and Gynecology at Tomo Riba Institute of Health and Medical Sciences, Naharlagun, Arunachal Pradesh, India, from November 2022 to October 2024. Approval from the Institutional Ethics Committee (Order No. TRIHMS/ETHICS/01-2019-20/55, dated 22nd October 2022) was obtained.

Inclusion criteria:

1. Consenting parturients.
2. Pregnant women with a known high-risk of developing hypertension with at least one of the following factors [13]:
    - First pregnancy at 18 years of age or ≥40 years of age.
    - Personal or family history of preeclampsia.
    - Primigravida.
    - Hyperplacentosis: gestational diabetes, multiple gestation, molar pregnancy.
    - Thrombophilia (Protein C&S deficiency, Factor 5 Leiden).
    - Pregnancy achieved through assisted reproductive technology.
    - Primi-paternity.
    - Obesity (Body Mass Index (BMI)>35 kg/m^2).

Exclusion criteria:

- Smoker.
- Foetal anomaly.
- Known cases of hypertension/diabetes before gestation or Non Steroidal Anti-Inflammatory Drugs (NSAIDs) abuse.
- History of autoimmune disease or Antiphospholipid Antibody Syndrome (APLA).
- Known cases of Chronic Kidney Disease (CKD), Cardiovascular Disorder (CVD), liver disease, or vascular disorder.

Sample size: Using the following formula:

$$n=Z\alpha\ [PQ/d^2]$$

Zα=standard normal deviation for a 95% confidence interval (1.96).

p=prevalence of preeclampsia of 6% in India [14].

q=1-p, when 'p' is in decimal terms (1-0.05=0.94).

d=precision of estimate, i.e., 5%.

The sample size calculated was 100 subjects.

Study Procedure

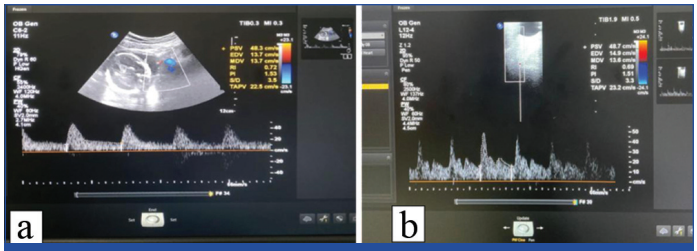
After obtaining consent, pregnant women attending the outpatient department or admitted to the obstetrics ward in the second trimester of pregnancy at TRIHMS were included in the study. Subjects underwent routine ultrasonography evaluation and were assessed for the PI, which is the ratio of maximum and minimum blood flow velocity to the mean blood flow velocity. The formula is as follows:

$$\left(\frac{\text{Vmax-Vmin}}{\text{V mean}} \text{ or } \frac{\text{Peak Systolic Flow-Peak Distolic Flow}}{\text{Mean Flow}}\right).$$

The doppler flow velocimetry was obtained as follows:

A. **Uterine artery doppler velocimetry:** To obtain uterine flow velocimetry, participants were instructed to lie down in a supine position. After proper exposure of the abdomen, a color Doppler scan using a curvilinear probe (4 MHz) was performed transabdominally. A longitudinal view focused on the lateral aspect of the lower uterine segment allowed for visualisation of the uterine artery as it branches off the internal iliac artery after bifurcating from the common iliac artery. The artery should be non compressible and pulsatile [Table/Fig-1a]. Recordings were made at the crossing between the uterine and external iliac arteries, as demonstrated using color flow Doppler on both sides. The cut-off for PI value was taken as ≥1.45, based on a previous study [15].

B. **Ophthalmic artery doppler velocimetry test:** Patients were examined in a supine position with a head tilt of approximately 15° after a rest period of at least 10 minutes. Following the application of a small amount of methylcellulose gel on the closed eyelid, the transducer (linear probe) was positioned horizontally without applying pressure to the orbit. Up-and-down tipping movements were performed to identify the ophthalmic artery at approximately 15 mm from the ocular globe via colour mapping. Using pulsed Doppler ultrasound, the double peak of the first and second systolic velocities of the ophthalmic artery was measured. The cut-off PI value for the right ophthalmic artery was taken as <1.76, as shown in [Table/Fig-1b] [11].



[Table/Fig-1]: a) Uterine artery; and b) Ophthalmic artery doppler velocimetry.

Participants were followed-up throughout pregnancy and delivery. The findings of PI were categorised as:

a) Normal mean uterine artery Doppler velocimetry (PI<1.45).

b) Abnormal mean uterine artery Doppler velocimetry (PI≥1.45).

c) Normal ophthalmic artery velocimetry (PI≥1.76).

d) Abnormal ophthalmic artery velocimetry (PI<1.76).

STATISTICAL ANALYSIS

All data were collected and entered into a Microsoft Excel sheet. Categorical data were described in percentages, while continuous data were presented as Mean±Standard Deviation (SD). The Chi-square test, Student's t-test, and ANOVA were used for analysis and the data were analysed using GraphPad Prism 10.1.3. A p-value <0.05 was considered statistically significant.

RESULTS

The age of participants ranged from 18 to 44 years, with a mean age of 26±5.01 years. The mean±SD of participants' weight, height, and BMI were 66.37±7.99 kg, 152.5±4.72 cm, and 28.48±6.35 kg/m^2, respectively. Seventy-two percent of the cohort were primigravid parturients, while the remaining 28% were multigravida [Table/Fig-2]. A total of 27 cases developed preeclampsia during this study. Two participants had more than one risk factor included in the study (as shown in [Table/Fig-2]). Both participants were primigravidae with multiple gestation; among them, the second participant conceived following assisted reproductive technology (an additional risk factor).

Parameters		Normal cases	PE	p-value
Age (years)		26.24±5.43	28±5.67	0.16*
Weight (Mean±SD kg)		66.66±8.33	66.15±6.82	0.70*
Height (cm)		151.88±4.47	153.8±4.81	0.06 *
BMI (kg/m^2)		28.97±4.03	27.93±2.84	0.21*
Gravida	Primigravida	60 (83.3%)	12 (16.7%)	0.004†
	Multigravida	13 (46.4%)	15 (53.6%)	

[Table/Fig-2]: Comparison of profile of normal and preeclampsia participants.
*t-test, †Chi-square

The cases with a previous history of preeclampsia and gestational diabetes mellitus had a propensity to develop preeclampsia of 100% [Table/Fig-3]. Non severe and severe preeclampsia occurred in 10 and 17 participants, respectively. The mean Systolic Blood Pressure (SBP) at the time of primary scanning and after 20 weeks of gestation in the severe group was 124.11±8.70 mmHg and 172.70±13.48 mmHg, while in the non severe group, it was 123.00±6.74 mmHg and 148.00±4.21 mmHg, respectively [Table/Fig-4]. The PI≥1.45 was found in 25.93% of patients developing preeclampsia and 12.33% in those with normal pregnancies; however, this difference was statistically not significant (p-value=0.13). The PI of the ophthalmic artery being less than 1.76 was found to be very highly significantly associated with the development of preeclampsia (p-value=0.0001) [Table/Fig-5].

Parameters	Cases	PE (Proportion)
1. Primigravida	72*	12 (167%)
2. Previous history of preeclampsia	10	10 (100%)
3. Family history of preeclampsia	09	03 (33%)
4. Gestational diabetes mellitus	02	02 (100%)
5. Use artificial reproductive technology	02*	01 (50%)
6. Multiple gestation	5*	02 (40%)
7. Primi-paternity	1	0
8. Molar pregnancy	2	0
9. Obesity	3	0
10. Others	1	0

[Table/Fig-3]: Risk factor and proportion of preeclampsia.
*Cases having 2 (two) or more risk factors together

Variables	Primary scanning			After 20 weeks of gestation			p-value
	Normal	Non severe	Severe	Normal	Non severe	Severe	
SBP Mean±SD	108.08± 8.76	123.00± 6.74	124.11± 8.70	111.09± 7.18	148.00± 4.21	172.70± 13.48	0.0001*
DBP Mean±SD	73.69± 6.97	85± 7.07	81.76± 8.08	74.93± 6.89	102± 7.88	114.23± 12.34	0.0002*

[Table/Fig-4]: Comparison of blood pressure at primary and 20 weeks' gestation USG scanning of PE.
*ANOVA

Parameters	Preeclampsia	Non-preeclampsia	p-value
PI uterine artery			
≥1.45	7 (25.93%)	9 (12.33%)	0.13 (NS)*
<1.45	20 (74.07%)	64 (87.67%)	
PI ophthalmic artery			
<1.76	23 (85%)	30 (41%)	0.0001 (HS)**
≥1.76	4 (14.81%)	43 (58.9%)	

[Table/Fig-5]: Uterine artery.
PI. *NS: Not Significant; **HS: Highly Significant by Chi-square test

The PI of the uterine artery had a sensitivity of 25% and specificity of 87%, with a Positive Predictive Value (PPV) of 43% and a Negative Predictive Value (NPV) of 76% at a cut-off value of ≥1.45. In contrast, the PI of the ophthalmic artery had a sensitivity of 85% and specificity of 58%, with a PPV of 43% and NPV of 91% at a cut-off value of <1.76 in predicting preeclampsia [Table/Fig-6].

Parameter	Sensitivity	Specificity	PPV	NPV	Likelihood ratio
Uterine artery	0.25	0.87	0.43	0.76	2.10
Ophthalmic artery	0.85	0.58	0.43	0.91	2.03

[Table/Fig-6]: Comparison of diagnostic accuracy indices with PI of Uterine and Ophthalmic arteries.

Of the participants who successfully delivered a live baby during this study, 91% of those with normal blood pressure had normal deliveries, whereas 36% of the cases that developed preeclampsia underwent caesarean sections. This difference was found to be statistically highly significant (p-value=0.0001) [Table/Fig-7]. Among the live babies delivered during this study, a total of 27 babies required admission to the Sick Neonatal Care Unit (SNCU): 5, 8, and 14 babies were born to parturients with normal pregnancies, non severe preeclampsia, and severe preeclampsia, respectively. Two foetal deaths were recorded during this study; one occurred in a case of normal pregnancy, and the other in a severe preeclamptic mother.

Parameters	Normal (n=71)	Non severe PE (n= 10)	Severe PE (n=17)	p-value
NVD	59 (91%)	2 (3%)	4 (6%)	0.0001 HS*
CS	12 (36%)	8 (24%)	13 (40%)	
Baby weight in Kg (Mean±SD)	2.9±3.4	2.4±0.80	2.2±0.82	ANOVA 0.0001 (HS)*
SNCU admission	5 (18.51%)	8 (29.63%)	14 (51.85%)	0.0001 (HS)*
Small For gestation	1 (14.29%)	0	6 (85.71%)	0.0016 (HS)*
Preterm	2 (11.77%)	5 (29.41%)	10 (58.82%)	0.0001 (HS)*
IUGR	0	3 (37.5%)	5 (62.5%)	0.0001 (HS)*

[Table/Fig-7]: Distribution of deliveries and neonatal outcome in live babies.
*HS: Highly significant; †NS: Not significant. Chi-square test was used, except baby weight where ANOVA was used. Included only babies delivered alive

DISCUSSION

Preeclampsia is a major cause of maternal and neonatal mortality and morbidity, especially in developing regions and low socio-economic areas. According to the International Federation of Gynecology and Obstetrics, the prevalence of preeclampsia is 2-5%, particularly in lower socio-economic strata [16]. In the current study, the prevalence of preeclampsia was found to be 2.7%, which aligns with the finding of the study conducted by Sapantzoglou I et al., who reported a prevalence of 2.7% [17].

The current study found a significantly higher occurrence of preeclampsia in multigravida participants (53%) compared to primigravida participants (16%) (p-value 0.004). This finding was consistent with the study by Setyorini D et al., but contradictory to the findings of Mandal J and Roy D and Maeda Y et al., who concluded that multigravidas are less prone to develop preeclampsia due to the desensitisation of antigens in previous pregnancies [18-20]. Individuals with a history of preeclampsia in previous pregnancies showed a higher propensity to develop preeclampsia, which was in line with studies conducted by Aracil Moreno I et al., and Jimoko B et al., who hypothesised that these patients have increased placental mass, leading to circulatory overload and placental hypoxia, which in turn may increase the risk of developing preeclampsia [21,22]. The current study also found an association between preeclampsia and gestational diabetes mellitus, which may be due to vascular pathophysiology, oxidative stress and inflammatory reaction, proportionately associated with the blood glucose levels of the parturient, along with genetic predisposition [14,23,24].

Seven cases with abnormal uterine artery Doppler PI values (≥1.45) developed preeclampsia, while nine remained normotensive after 20 weeks of gestation. In contrast, 64 participants had normal Doppler PI values (<1.45) and did not develop preeclampsia, while 20 did. However, this finding was not statistically significant (p-value 0.13). Therefore, this study aligns with the findings of Pedroso MA et al., who inferred that the use of uterine artery Doppler as a single predictive test for preeclampsia has poor accuracy; however, it contradicts the findings of Verma D and Gupta S who concluded that uterine artery Doppler is a significant predictor of preeclampsia [15,25].

Participants with ophthalmic artery PI values <1.76 were associated with a higher number of cases developing preeclampsia (23 out of 53), whereas those with PI values ≥1.76 had fewer cases that developed preeclampsia (4 out of 47 participants). This result was

statistically highly significant (p-value=0.0001). Thus, present study support the findings revealed by Kumari N et al., which suggest that ophthalmic artery Doppler PI could be used as a reliable marker for preeclampsia [26]. This finding seems to contradict the results of the study conducted by Praciano de Souza PC et al., who concluded that maternal ophthalmic artery Doppler did not significantly increase the preeclampsia detection rate during the second trimester scan [27].

In this study, the sensitivity of uterine artery PI was found to be 25%, and the specificity was 87% at a cut-off value of ≥1.45. The sensitivity appeared to be lower, whereas the specificity was higher compared to a recent study done by Ali AM et al., which reported a sensitivity for uterine artery PI of 89% and a specificity of 76.92% [28]. However, it was comparable to the finding of the study by Verma D and Gupta S, where the sensitivity (62%) of uterine artery PI was lower, while the specificity (87%) was higher [15].

The ophthalmic artery PI had a sensitivity of 85% and a specificity of 58% at a cut-off value of <1.76 in predicting preeclampsia. The current study agrees with the findings of Kalafat E et al., who concluded that ophthalmic artery Doppler is a simple, accurate and objective technique with standalone predictive value for the development of early-onset preeclampsia, equivalent to that of uterine artery Doppler evaluation [29].

The preeclampsia participants had a higher rate of caesarean delivery compared to normal deliveries in the current study. This finding aligns with the study by Chilumula K et al., where they found that women with hypertensive disorders are more likely to have a caesarean section [30]. Patients with severe preeclampsia and abnormal uterine and ophthalmic artery Doppler values had poor neonatal outcomes, such as preterm delivery, low birth weight, Intrauterine Growth Restriction (IUGR), and admissions to the Sick Neonatal Care Unit (SNCU). Thus, the authors agree with the conclusions of Li N et al., and Martin AM et al., who suggested that abnormal Doppler flow velocimetry can be used as a predictor of adverse perinatal outcomes, including Small for Gestational Age (SGA), preterm delivery, IUGR and SNCU admission [31,32].

The PI of the ophthalmic artery shows higher sensitivity and lower specificity compared to the uterine artery PI, which exhibits lower sensitivity and higher specificity. Therefore, present study agree with the findings of Lau KGY et al., that ophthalmic artery Doppler can be a good predictor of foetal outcomes, despite the lack of extensive studies on ophthalmic artery Doppler in normal pregnancies [33].

Limitation(s)

This study was a prospective cohort study that lacked blinding and randomisation. The authors acknowledge that the findings may not be generalisable, as only participants with known risk factors were included. A randomised study with a larger number of participants and multivariate analysis should be conducted. Sample size concerns: While the authors calculated a sample size of 100, this may be underpowered for some of the subgroup analyses conducted. The small numbers in certain risk categories (e.g., 2 cases of gestational diabetes) make it difficult to draw meaningful conclusions about these specific risk factors. Additionally, the uterine artery Doppler was performed transabdominally, which was less precise than transvaginal Doppler in some cases. Optimal cut-off values for this population via ROC curve analysis were not performed.

CONCLUSION(S)

Ophthalmic artery Doppler velocimetry is a better predictor of preeclampsia compared to uterine artery Doppler velocimetry. The authors conclude that Doppler flow velocimetry is easily accessible, non invasive, cost-effective and less time-consuming for screening high-risk pregnancies and can be implemented widely, even in remote areas. In cases where velocimetry results are abnormal, the parturient should be managed with heightened vigilance and timely serial follow-up for preeclampsia.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jun 11, 2025
- Manual Googling: Jul 05, 2025
- iThenticate Software: Jul 08, 2025 (16%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Jun 08, 2025**
Date of Peer Review: **Jun 26, 2025**
Date of Acceptance: **Jul 10, 2025**
Date of Publishing: **Aug 01, 2025**