

Role of Uterine Artery Doppler at 11-14 Weeks of Pregnancy in Early Prediction of Preeclampsia: A Prospective Cohort Study

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ABSTRACT

Introduction: Doppler ultrasonography, by comparing systolic and diastolic waveforms helps in assessment of uteroplacental circulation. Since preeclampsia has ethnic and geographical variations, it is important to understand the prediction modalities in various populations.

Aim: To investigate the role of elevated Pulsatility Index (PI) and presence of diastolic notch using uterine artery doppler in early pregnancy in predicting development of preeclampsia among pregnant women.

Materials and Methods: A prospective cohort study was conducted on pregnant females visiting the antenatal clinic or Outpatient Department or admitted in the Department of Obstetrics and Gynaecology at People's College of Medical Sciences and Research Centre, Bhopal, Madhya Pradesh, India, from November 2019 to October 2021. All cases were subjected to uterine artery doppler study, between 11-14 weeks of pregnancy, to note pulsatility index and diastolic notch. All the participants were then screened periodically during their antenatal visits for development of features of preeclampsia and were followed-up monthly upto 20 weeks, every 15 days upto 32 weeks and then, weekly till delivery. Pregnancy

outcome were measured in terms of presence or absence of preeclampsia. Data was compiled using Microsoft Excel and analysed using Statistical Package for Social Sciences (SPSS) IBM software version 20.0. Categorical data was expressed as frequency and proportions, whereas, continuous data was expressed as mean and standard deviation.

Results: The present study was conducted on a total of 116 cases with the mean age of 26.75±4.31 years. Out of 116 cases, 26 cases developed preeclampsia. Diastolic notch was present in 17 cases (65.4%) patients with preeclampsia and 23 cases (25.6%) non preeclampsia patients. Pulsatility index of more than 1.71 was noted in 14 cases (53.8%) cases with preeclampsia, whereas, 87 cases (96.7%) with non preeclampsia had pulsatility index of less than 1.71. The specificity of diastolic notch 74.4% where as that of pulsatility index was 96.7% and the diagnostic accuracy of diastolic notch 72.4%, whereas, that of pulsatility index was 87.1%.

Conclusion: Uterine artery doppler is a promising tool for predicting development of preeclampsia by analysing both PI as well as diastolic notch in uterine artery. Doppler had high overall diagnostic accuracy for preeclampsia.

Keywords: Antenatal, Diastolic notch, Early second trimester, Preeclampsia third trimester, Pulsatility index

INTRODUCTION

Hypertensive disorders of pregnancy are the second most common cause of maternal and perinatal morbidity and mortality globally. Hypertensive disorders complicate approximately 5 to 10% of all pregnancies worldwide [1]. However in India the incidence of hypertensive disorders of pregnancy is 10 to 12% [2]. Among various hypertensive disorders, Preeclampsia (PE) characterised by new onset hypertension and proteinuria (more than 20 weeks of gestation) is most common cause of maternal morbidity and mortality [3,4]. The key element of providing antenatal care is identification of high risk cases early (preferably in first trimester) so as to initiate management and minimise the risk of adverse pregnancy outcome [5]. A wide range of biomarkers for prediction of preeclampsia have been recommended such as maternal characteristics (body mass index, co-morbidities), a disintegrin and metalloproteinase 12 (ADAM12), Pregnancy Associated Plasma Protein A (PAPP-A), soluble Fms like tyrosine kinase 1 (sFlt1), placental growth factor, Placental Protein 13 (PP13), doppler ultrasonography [6,7].

Doppler Ultrasound (USG) is a non invasive invaluable tool in management of high risk cases. Though, the direct assessment of trophoblastic invasion could not be observed, doppler ultrasonography, by comparing systolic and diastolic waveforms helps in assessment of uteroplacental circulation [8,9]. Uterine artery is the most commonly studied vessel for doppler evaluation. The parameters used for assessment for uteroplacental insufficiency includes early diastolic notch, pulsatility or resistance index of uterine artery [10,11]. Literature suggests that doppler ultrasonography of uterine

artery for detection of preeclampsia is very useful during 12 to 16 weeks of gestation [12,13]. However, some studies highlighted its utility in third trimester for predicting haemodynamic alterations and uteroplacental insufficiencies [14].

Early identification of at risk population especially during first trimester and early second trimester might be helpful in commencing appropriate management strategies, thereby reducing the risk of adverse maternal and perinatal outcome [15,16]. With the above background, authors aimed to investigate the role of elevated Pulsatility Index (PI) and presence of diastolic notch using uterine artery doppler, in early pregnancy (late first trimester/or early second trimester) in predicting development of preeclampsia among the pregnant women visiting antenatal clinic in a tertiary care hospital.

MATERIALS AND METHODS

A prospective cohort study was conducted on pregnant females visiting the antenatal clinic or Outpatient Department or admitted in the Department of Obstetrics and Gynaecology at People's College of Medical Sciences and Research Centre, Bhopal, Madhya Pradesh, India, from November 2019 to October 2021. Institute Ethical Committee approval was obtained {IEC No.:PCMS/OD/2019/1440(4)} and written informed consent from all study participants were taken.

Sample size calculation: As per formula,

$$N = Z\alpha^2 [pxq] / d^2$$

Where, $Z\alpha$ is from probability table and 2 Standard Errors (SE) corresponds to 1.96.

p was prevalence of preeclampsia i.e. 5.4% (approximately 6%). Prevalence was included from National Health Portal of India. (<https://www.nhp.gov.in/disease/gynaecology-and-obstetrics/preeclampsia>).

q was 1-p, when p is in decimal terms (1-0.06=0.94).

d was precision of estimate i.e. 5%

Substituting these values,

$$N=(1.96)^2[0.06*0.94]/(0.05)^2=90.24$$

$$\text{Actual sample size}=90.24+10\% \text{ of } 90.24=100$$

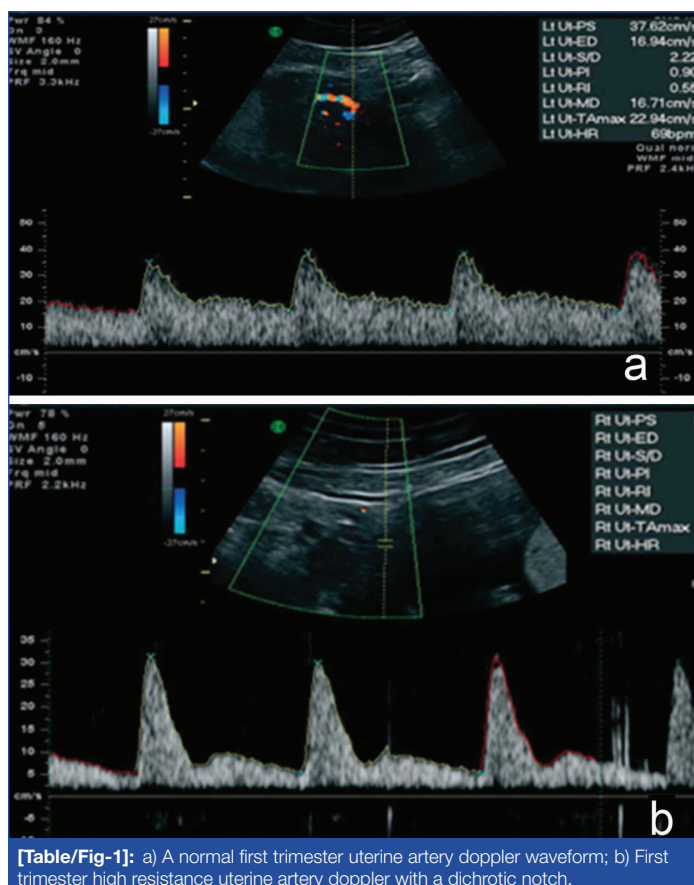
Inclusion and Exclusion criteria: All females with singleton pregnancy between 11-14 weeks of gestation were included in the study. Patients with gross foetal malformation on Ultrasonography (USG) (like anencephaly, meningomyelocele), were on treatment with aspirin, heparin or antihypertensives, known case of essential hypertension, history of Pregnancy Induced Hypertension (PIH) in previous pregnancy, with multiple pregnancy, who had miscarriage on follow-up, critically ill patients were excluded from the study.

Detailed data regarding socio-demographic variables such as age, education, socio-economic status were obtained from all the study participants [17]. Obstetric history was obtained in detail and any history of complications in previous pregnancy was noted. Further, all the cases were subjected to detailed general, systemic and obstetric examination. Blood pressure was recorded after 10 minutes rest, at 45 degrees tilt and cuff at the level of heart. Routine investigations were conducted including antenatal investigation, liver function test, kidney function test, blood test, Bleeding Time (BT), Clotting Time (CT), activated partial thromboplastin time/international normalised ratio, prothrombin time, fibrin degradation products.

Procedure

All cases were subjected to doppler study, between 11-14 weeks of pregnancy (using convex 4 MHz probe), to note the following two indices [Table/Fig-1a,b]:

- **Pulsatility Index (PI):** Parameter obtained from maximum, minimum and blood flow velocity in uterine artery during a cardiac cycle. In the present study, cut-off of PI value was taken as >1.71 [18].



[Table/Fig-1]: a) A normal first trimester uterine artery doppler waveform; b) First trimester high resistance uterine artery doppler with a dichotic notch.

$$PI=(V_{max}-V_{min})/(V_{mean})$$

Or

$$PI=(\text{peak systolic flow}-\text{peak diastolic flow})/(\text{mean flow})$$

PI of right and left uterine arteries was measured and mean PI was calculated.

- **Diastolic notch:** Diastolic notching was described as a presence of a trough like notch between systolic and diastolic phases in uterine arterial doppler study. Bilateral uterine arteries were seen for presence/absence of diastolic notch.

All the participants were then screened periodically during their antenatal visits for development of features of preeclampsia like headache, blurring of vision, epigastric pain, vomiting, elevated blood pressure, presence of urine albumin, presence of pedal edema or abdominal wall oedema and weight gain [17]. Antenatal care, investigations and treatment were done as per routine protocol practiced in the department.

Patients were periodically followed-up monthly upto 20 weeks, every 15 days upto 32 weeks and then, weekly till delivery. Pregnancy and neonatal outcome were measured in terms of pregnancy complications.

STATISTICAL ANALYSIS

Data was compiled using Microsoft Excel and analysed using Statistical Package for Social Sciences (SPSS) IBM software version 20.0. Categorical data was expressed as frequency and proportions where as continuous data was expressed as mean and standard. Association of doppler findings with outcome was assessed using Chi-square test. The p-value <0.05 was considered statistically significant.

RESULTS

The present study was conducted on a total of 116 cases with the mean age of 26.75±4.31 years. Out of 116 cases, 26 cases developed preeclampsia. The incidence of preeclampsia was higher in females with less education and nulliparous females. The observed difference in gestational age at delivery between two groups was statistically significant (p-value=0.01) [Table/Fig-2].

Parameters	Non preeclampsia (n=90)	Preeclampsia (n=26)	Total (n=116)	p-value
Age (years)				
≤20	7 (7.8%)	2 (7.7%)	9 (7.8%)	0.45
21-30	67 (74.4%)	22 (84.6%)	89 (76.7%)	
>30	16 (17.8%)	2 (7.7%)	18 (15.5%)	
Education				
Primary	11 (12.2%)	1 (3.8%)	12 (10.3%)	0.01
Secondary	37 (41.1%)	20 (76.9%)	57 (49.1%)	
Intermediate	39 (43.3%)	5 (19.2%)	44 (37.9%)	
Graduation	3 (3.3%)	0 (0%)	3 (2.6%)	
Parity				
0	28 (31.1%)	15 (57.7%)	43 (37.1%)	0.04
1	56 (62.2%)	10 (38.5%)	66 (56.9%)	
>1	6 (6.7%)	1 (3.8%)	7 (6%)	
Mean gestational age (in weeks)	38.44±1.49	36.65±1.52	38.04±1.67	0.01

[Table/Fig-2]: Association between preeclampsia and baseline variables. p-value <0.05 was considered as statistically significant.

Diastolic notch was present in 65.4% patients with preeclampsia and 25.6% non preeclampsia patients. Pulsatility index of more than 1.71 was noted in 53.8% cases with preeclampsia where as 96.7% cases with non preeclampsia had PI of less than 1.71. The observed difference in the diastolic notch as well as PI between preeclampsia and non preeclampsia cases was statistically significant (p-value=0.01) [Table/Fig-3].

Doppler		Non preeclampsia (n, %)	Preeclampsia (n, %)	p-value
Diastolic notch (11-14 wk)	Present	23 (25.6%)	17 (65.4%)	0.01
	Absent	67 (74.4%)	9 (34.6%)	
Pulsatility index	<1.71	87 (96.7%)	12 (46.2%)	0.01
	≥1.71	3 (3.3%)	14 (53.8%)	

[Table/Fig-3]: Association of diastolic notch and pulsatility index in non preeclampsia patients (n=90) and preeclampsia patients (n=26). p-value <0.05 was considered as statistically significant

The sensitivity of diastolic notch in diagnosis of preeclampsia was 65.4% whereas, that of PI was 53.8% [Table/Fig-4].

Pulsatility index of more than 1.7 was significantly associated with adverse foetal outcome in terms of preterm delivery, Intrauterine Growth Restriction (IUGR) and Neonatal Intensive Care Unit (NICU) admission (p-value=0.001) and diastolic notch was associated with significantly higher proportions of foetus with intrauterine growth restriction (27.5%) [Table/Fig-5].

Parameters	Sensitivity	Specificity	PPV	NPV	Diagnostic accuracy
Diastolic notch	65.40%	74.40%	42.50%	88.20%	72.40%
Pulsatility index	53.80%	96.70%	88.20%	87.90%	87.10%

[Table/Fig-4]: Sensitivity and specificity of diastolic notch in diagnosis of preeclampsia. PPV: Positive predictive value; NPV: Negative predictive value

Foetal outcome	Pulsatility index			Diastolic notch		
	<1.7 (n=99) (n, %)	≥1.7 (n=17) (n, %)	p-value	Absent (n=76) (n, %)	Present (n=40) (n, %)	p-value
Preterm	6 (6.1)	5 (29.4)	0.001	5 (6.6)	6 (15)	0.12
Intrauterine Growth Restriction (IUGR)	6 (6.1)	13 (76.5)	0.001	8 (10.5)	11 (27.5)	0.02
Neonatal Intensive Care Unit (NICU) Admission	24 (24.2)	12 (70.6)	0.001	23 (30.3)	13 (32.5)	0.81

[Table/Fig-5]: Association of pulsatility index and diastolic notch with foetal outcome. p-value <0.05 was considered as statistically significant

In present study, 73.3% and 23.3% non preeclampsia cases had normal doppler findings and presence of diastolic notch respectively. In contrast, 19.2% preeclamptic cases had diastolic notch, 7.7% cases had only raised PI and 46.2% cases had both diastolic notch as well as PI (p-value=0.001) [Table/Fig-6].

Doppler findings	Non preeclampsia (n=90) (n, %)	Preeclampsia (n=26) (n, %)	Total (n, %)
Normal	66 (73.3)	7 (26.9)	73 (62.9)
Only Diastolic notch	21 (23.3)	5 (19.2)	26 (22.4)
Only PI>1.7	1 (1.1)	2 (7.7)	3 (2.6)
Both (Doppler notch and PI >1.7)	2 (2.2)	12 (46.2)	14 (12.1)
χ^2	42.7		
p-value	0.001		

[Table/Fig-6]: Association of overall doppler findings (doppler notch and pulsatility index) with preeclampsia. p-value <0.05 was considered as statistically significant

Pulsatility index of more than 1.71 was noted in 14 cases (53.8% cases) with preeclampsia where as 87 cases (96.7% cases) with non preeclampsia had PI <1.71. The observed difference in the PI between preeclampsia and non preeclampsia cases was statistically significant (p-value=0.001) [Table/Fig-7].

Pulsatility index (11-14 WK)	Non preeclampsia (n=90)	Preeclampsia (n=26)	Total (n=116)
<1.71	87 (96.7%)	12 (46.2%)	99 (85.3%)
≥1.71	3 (3.3%)	14 (53.8%)	17 (14.7%)

Mean	1.47±0.21	1.75±0.37	1.54±0.28
χ^2	3.7		
p-value	0.001		

[Table/Fig-7]: Association of pulsatility index with preeclampsia.

DISCUSSION

Preeclampsia is one of the most common cause associated with increased maternal morbidity and mortality all over the world. To reduce the associated complications and maternal morbidity and mortality, it is important to identify and manage the preeclampsia early so as to minimise the risk of adverse pregnancy outcome. USG doppler has been recommended as an invaluable tool for assessment of uteroplacental circulation and early identification of preeclampsia [1]. Three parameters are identified and linked with uteroplacental insufficiency and markers of preeclampsia. These include resistance index, pulsatility index and diastolic notch [11].

Kennedy AM and Woodward PJ, documented that diastolic notch during early pregnancy is a normal finding, which begin to disappear by 13 weeks of gestation. Persistence of diastolic notch after 13 weeks may be considered abnormal. And diastolic flow is established clearly by 20 weeks [15,19,20]. Early diastolic notching represent the reduced diastolic velocities as compared to notching in later part of diastole [21]. Bilateral notching is of high significance as compared to unilateral notching; but unilateral notching especially on ipsilateral side of the placental attachment also implies significant association with preeclampsia [20]. In present study, diastolic notch was observed insignificantly higher proportions of patients with preeclampsia (65.4%) as compared to those with non preeclamptic patients (25.6%). The current study findings were supported by Bindal J and Chugh N, in which the authors documented diastolic notch in 68.18% cases with preeclampsia [18]. Sultana S et al., also observed diastolic notching in significantly higher proportion of females with preeclampsia (90%) as compared to those with normal pregnancy (5%) [22].

In present study, pulsatility index was raised (>1.71) in 53.8% cases with preeclampsia as compared to 3.3% cases without preeclampsia. Higher in preeclampsia (1.75±0.37) as compared to normal females (1.47±0.21). Bindal J and Chugh N, also documented that significantly higher proportions of cases with preeclampsia had PI>1.71 (p-value <0.05). Concordant findings were documented by Köpük ŞY et al., where the authors documented significantly higher proportion so, patients with high PI values in preeclampsia group (p-value=0.023) [18,23].

In the present study, both pulsatility index and diastolic notch were observed in 46.2% cases of preeclampsia and 2.2% cases with non preeclampsia. However, only diastolic notch and only high pulsatility index was documented in 19.2% and 7.7% cases with preeclampsia. In contrast Bindal J and Chugh N, documented presence of both pulsatility index and diastolic notch in only 12% cases [18]. Gomez O et al., documented significantly higher PI and higher prevalence of bilateral notching in patients with preeclampsia [10].

In present study, sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of diastolic notch for diagnosis of preeclampsia was 65.4%, 74.4%, 42.5% and 88.2% respectively with diagnostic accuracy of 72.4%. Similarly, sensitivity of PI at cut-off of 1.71 was 53.8% whereas, specificity, PPV, NPV and diagnostic accuracy of PI was higher as compared to diastolic notch. Köpük ŞY et al., documented the sensitivity of 42.31% and specificity of 82.10% at the cut-off of >2.23 for detecting preeclampsia [23]. Carbillon L, reported high sensitivity of uterine artery doppler at 11-14 weeks for prediction of preeclampsia with low PPV [24]. Narang S et al., also showed sensitivity and specificity of PI at 11-14 weeks of pregnancy for detection of preeclampsia as 75.9% and 79.6% respectively [Table/Fig-8] [10,18,23,25].

Author	Indicator	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Gomez O et al., (2005) [10]	PI	24%	95%	11.3%	97.9%
Bindal J and Chugh N, (2016) [18]	Notch+PI	75%	60.8%	57.14%	77.78%
Narang S et al., (2016) [25]	PI	75.9%	79.6%	-	-
Köpük ŞY et al., (2019) [23]	PI	42.3%	82.1%	-	-
Present study, 2022	Notch only	65.4%	74.4%	42.5%	88.2%
	PI only	53.8%	96.7%	88.2%	87.9%

[Table/Fig-8]: Comparison of various study with present study [10,18,23,25].

Limitation(s)

Interobserver error in doppler can be a limiting factor and should be considered before starting any intervention.

CONCLUSION(S)

Uterine artery doppler is a promising tool for predicting high risk cases for development of preeclampsia. Both PI as well as diastolic notching uterine artery doppler had high overall diagnostic accuracy for preeclampsia. However, low sensitivity of PI (>1.71) is one of the limiting factor for its use. Thus, doppler of uterine artery can be considered as a good screening method for predicting the risk of preeclampsia at 11-14 weeks of gestation.

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