

# Role of Uterine Artery Doppler in Prediction of Preeclampsia: A Prospective Analytical Study

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## ABSTRACT

**Introduction:** Preeclampsia is pregnancy specific hypertensive disorder of pregnancy which is associated with both high maternal and perinatal morbidity and mortality. Timely prediction and management in time, are the two key factors for prevention of these morbidities and mortalities. The aim of present study was to evaluate role of uterine artery doppler in prediction of preeclampsia in second and third trimester of pregnancy in Indian setting. **Materials and methods:** This was a prospective analytical study done at department of Obstetrics and Gynaecology, King George Medical university, Lucknow over a period of one year. After ethical approval (Institutional Ethics Committee, KGMU, Lucknow, Ref. Code: 92<sup>nd</sup> ECM II B- thesis P/29.) and informed consent from every patient, recruitment was done. Group I had 120 normotensive patients and Group 2 had 100 preeclampsia patients at time of enrollment. Bilateral uterine artery doppler was done for every patient and patient were further followed for maternal and perinatal outcome. **Results:** Total 220 patients were studied. In Group 1, 15 patients developed preeclampsia. Both groups were comparable for maternal age and parity. However, BMI was found to be significantly higher in the patients of Preeclampsia group. Uterine artery doppler, showed statistically significant difference and it was high in preeclampsia group. It had high negative predictive value. Gestation of termination was significantly lower in preeclampsia group. Fetal birth weight was significantly lower in preeclampsia group. **Conclusion:** Uterine artery doppler is a non-invasive test with high negative predictive value which should be utilized for prediction of preeclampsia for all pregnant patients.

**Key words:** Preeclampsia, Uterine artery doppler, Hypertension in pregnancy.

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## INTRODUCTION

Hypertensive disorder remains a primary cause of maternal and perinatal morbidity and mortality.<sup>1</sup> Approximately 10% of all maternal complication are associated with hypertensive disorders of pregnancy.<sup>2</sup> Preeclampsia is an important type of hypertensive disorder of pregnancy. In India, the incidence of preeclampsia is reported to be 8-10% among the pregnant women.<sup>3,4</sup> Preeclampsia is a hypertensive disease associated with pregnancy with multisystem

involvement. It is a disorder of vascular endothelial dysfunction and vasospasm that appear after 20 weeks of gestation and can present as late as 4-6 weeks postpartum. In preeclampsia there is abnormal placentation will lead to endothelial dysfunction. However exact prediction for preeclampsia is not possible till date. Following are various clinical, biochemical and biophysical test available for prediction of preeclampsia.

## Predictive test for development of Preeclampsia.<sup>5,6</sup>

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Testing related to	Examples
Placental perfusion/vascular resistance	Roll – over test, isometric handgrip or cold pressor test, pressor response to aerobic exercise, angiotensin -II infusion, midtrimester mean arterial pressure, platelet angiotensin – II binding, rennin, 24-hr ambulatory blood pressure monitoring, uterine artery or fetal transcranial Doppler velocimetry

Fetal – placental unit endocrine dysfunction	Human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), estriol, pregnancy – associated protein A (PAPP A), inhibin – A, activin A, placental protein 13, corticotrophin-releasing hormone, a disintegrin, ADAM-12, kisspeptin
Renal dysfunction	Serum uric acid, microalbuminuria, urinary calcium or kallikrein, microtransferrinuria, N-acetyl-β-glucosaminidase, cystatin C podocyturia
Endothelial dysfunction / oxidant stress	Platelet count and activation, fibronectin, endothelial adhesion molecules, prostaglandin, prostacyclin, MMP-9, thromboxane, C-reactive protein, cytokines, endothelin, neurokinin B, homocysteinine, lipids, insulin resistance, antiphospholipid antibodies, plasminogen activator inhibitor (PAI), leptin, p-selectin, angiogenic factors such as placental growth factor (PIGF),
Others	Antithrombin- III (AT-3) atrial natriuretic peptide (ANP), β2-microglobulin, haptoglobin, transferrin, ferritin, 25-hydroxyvitamin D, genetic markers, cell free fetal DNA, serum and urine proteomics and metabolomic markers, hepatic aminotransferase

In various studies it is found that Pregnancy is associated with profound hemodynamic changes, such as systemic vascular resistance remains lower throughout pregnancy and arterial blood pressure shows a progressive fall in the first and middle trimesters, whereas cardiac output and heart rate slowly increase to a plateau in second trimester.<sup>7,8</sup> The mechanisms responsible for the pregnancy-associated vasodilatation are not yet fully understood, but recent data suggest endothelium-derived relaxing factor or nitric oxide (NO) as a chief mediator for the fall in vascular resistance.<sup>9-11</sup> In animal models, NO synthesis is increased in pregnancy.<sup>12-16</sup>

In humans, however, the role of NO as a mediator of the reduction in systemic vascular resistance remains disputed<sup>16</sup>. *In vitro*, in response to shear stress, a known stimulus for NO release which lead to increased relaxation of small subcutaneous arteries in pregnant women.<sup>17</sup> *In vivo* NG-monomethyl-L-arginine(L-NMMA), an NO synthase inhibitor, produces major reduction in blood flow in pregnant than in non - pregnant women, indicating a higher NO activity during pregnancy.<sup>18</sup> In pregnant women there are two waves of trophoblastic invasion during the development of placenta.

1<sup>st</sup> wave (6-12 weeks period of gestation) of invasion of Spiral Arteries within the Decidua.

2<sup>nd</sup> wave (16-22 weeks)- Endovascular Trophoblasts Reaching the Myometrial Portion of the Spiral

Arteries.<sup>19</sup> Inadequate trophoblastic invasion of second wave leads to poor placentation which is responsible for pathophysiology of preeclampsia, it helps in diagnosis of early-onset PE (onset of clinical symptoms before 34 weeks of pregnancy) and it can be assessed by the Doppler velocimetry of uterine arteries The aim of present study was to evaluate, the uterine artery doppler for prediction of preeclampsia in second and third trimester of pregnancy.

## MATERIALS AND METHODS

The prospective analytical study was conducted in Department of Obstetrics and Gynecology, in collaboration with Department of Radiodiagnosis, KGMU, Lucknow over a period of one year. Sample size was calculated on the basis of average variation in Uterine Artery PI (UtA-PI) between gestation periods of comparison in normal and pre eclamptic women and considering several parameters of investigation using the formula

$$n = \frac{(z_{\alpha} + z_{\beta})^2 + (\sigma_1^2 + \sigma_2^2)}{d^2}$$

$$n' = kn$$

Where  $\sigma_1 = 0.196$  The average SD of UtA-PI between gestation periods of comparison in normal women

$\sigma_2 = 0.145$   $\sigma_1 = 0.28$  The average SD of UtA-PI between gestation periods of comparison in pre eclamptic women

Ethical approval was obtained from Institutional Ethics Committee, KGMU, Lucknow, Ref. Code: 92<sup>nd</sup> ECM II B-thesis P/29. To begin with 120 women in control group and 100 women in case group were enrolled for study with inclusion criteria of age 18-45 years, normotensive and preeclamptic patients (20-40 weeks gestation) and patient willing to participate, were enrolled in the study. Patients with history of Hypertension /Diabetes before gestation or NSAID abuse, H/O autoimmune disease, APLA, known c/o CKD (Chronic Kidney Disease), CVD (Cardiovascular Disorder), vascular disorder and patient not willing to participate in study were excluded. Written informed consent to participate in study was taken from each woman. All women who fulfilled the inclusion criteria and gave consent were subjected to detailed personal history and obstetrical history. For Preeclampsia diagnosis, have been used in study as per (ACOG guideline).<sup>18</sup> Elevation of the arterial pressure after 20 weeks of gestational age SBP  $\geq$  140 or DBP  $\geq$  90 mmHg observed at two measurements with a 4-hr interval, proteinuria (1+ or above at proteinuria tape or 24hr proteinuria  $>$  0.3 g/24 hr) with or without signs/

symptoms, thrombocytopenia <1,00,000/ul, impaired liver function (twice than normal), severe persistent rt. upper quadrant pain or epigastric pain, progressive renal insufficiency, new-onset cerebral or visual disturbances. Out of 120 normotensive women, 100 remained normotensives till delivery and they were categorized as control group (Group I) 100 preeclamptic pregnant women comprised of (Group II). 15 women who develop preeclampsia in follow up were not included in study. 5 women were lost to follow up. After recruitment, demographic characteristic of all women was entered and subjected for colour doppler of bilateral uterine artery. For uterine artery Doppler, USG machine Toshiba and 3-7 MHZ transabdominal curvilinear transducer was used. Colour flow Doppler was used to identify each uterine artery. The wall filter was set at low value (50–60 Hz) and the angle of insonation was kept below 20°. Pulsed wave Doppler with a gate size of 2 mm was placed over uterine artery about 1 cm below the crossover point of the uterine artery and the external iliac artery to generate the spectral wave pattern. The waveform was recruited using an automated trace of at least 3 consecutive wave-form. RI, PI, S/D ratio were calculated and mean was obtained. Also, a unilateral or bilateral notch was recorded in diastolic wave, if present in uterine artery Doppler. All patients were followed till delivery and maternal fetal outcome were noted. In Maternal outcome, patient developing preeclampsia during the study, need of antihypertensive in preeclampsia group, severity of disease, period of gestation for termination, mode of delivery, maternal morbidity and mortality were noted. For Fetal outcome birth weight, need of NICU, NNU admission were noted. The data was expressed as mean and standard deviation (SD) or median, range and percentage as appropriate. All the categorical data was compared by using chi square test. Continuous variables in two groups were compared by *t*-test. More than two variables were analyzed by one way ANOVA followed by Tukey's post hoc test. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were used for diagnosing of preeclampsia by uterine artery Doppler. The *p*-value <0.05 was considered as significant. The statistical analysis was done using SPSS 26.0 version (Chicago, Inc., USA) windows software.

## RESULTS

In duration of one year period, total of 200 women were studied. The group of women who develop preeclampsia, had higher uterine artery PI ( $1.11 \pm 0.43$ ) and difference been statistically significant (Table 1).

**Table 1: Uterine Artery Doppler velocimetry between pregnant women in group I and group II.**

Ultrasound Finding	Group I (n = 100)	Group II (n = 100)	<sup>1</sup> <i>p</i> -Value
<b>S/D</b>			
Right	2.20±0.77	2.51±1.01	0.017*
Left	2.39±0.73	2.54±0.88	0.177
Average S/D	2.29±0.68	2.53±0.87	0.038*
<b>PI</b>			
Right	0.92±0.63	1.13±0.47	0.008*
Left	0.89±0.35	1.09±0.43	<0.001*
Average PI	0.90±0.40	1.11±0.43	<0.001*
<b>RI</b>			
Right	0.58±0.36	0.59±0.21	0.746
Left	0.64±0.47	0.61±0.19	0.624
Average RI	0.61±0.40	0.60±0.19	0.899

\*=Significant

Table 2 shows that the more is severity of preeclampsia, the higher are the values of PI. The cut-off value for Uterine artery PI was 0.98 (median) to make a diagnosis of preeclampsia. With these cut-off values, Uterine artery PI had more sensitivity of 61.2%, specificity of 70.4%, PPV of 79.0% and NPV of 90.0% in the diagnosis of preeclampsia (Table 3). These tests were demonstrating the accuracy of risk factors. Uterine artery PI was showed significant large area under the curve (AUC) on the ROC curve as shown in Figure 1. On comparing the outcome, it was found that because of preeclampsia, more preterm deliveries are occurring and it been statistically significant. Beyond preterm, low birth weight was also more prevalent in preeclampsia group (Table 4).

## DISCUSSION

Preeclampsia is one of the leading causes of maternal and fetal morbidity and mortality that affects 8 to 10 % of pregnancy.<sup>3</sup> Preeclampsia is a pregnancy specific disorder which is diagnosed after 20 weeks of gestational age with new onset hypertension and proteinuria. Poor placentation, a consequence of inadequate trophoblastic invasion is one of the key events of preeclampsia and can be evaluated by the Doppler velocimetry of uterine arteries.<sup>19,20</sup> In present study, mean age of the patients was  $26.33 \pm 3.44$  years for group I and  $27.54 \pm 5.15$  for group II, which was comparable. The majority of patients were nulliparous in both the groups (62% patient in group I and 55 % in group II). Mean BMI was statistically different in two groups with mean BMI of  $24.50 \pm 2.37$  in group I and  $25.34 \pm 2.91$  in group

**Table 2: Intra group comparison (Tukey Post-Hoc) of Uterine artery PI in between Group I, Non-Severe Preeclampsia (Group II a) and Severe Preeclampsia (Group II b) patients.**

Gestational age	Group I Vs Group II a		Group I Vs Group II b		Group II a Vs Group II b	
	Mean Difference	p-Value	Mean Difference	p-Value	Mean Difference	p-Value
20-28 weeks	-0.07	0.90	-0.16	0.63	-0.09	0.91
29-34 weeks	-0.19	0.25	-0.32	0.03*	-0.13	0.43
>34 weeks	-0.34	0.21	-0.23	0.66	0.24	0.89

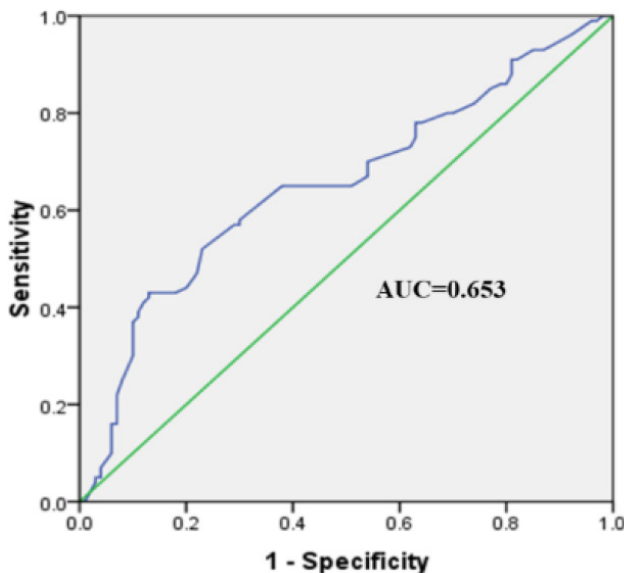
\*=Significant

**Table 3: Sensitivity, specificity positive productive value (PPV) and negative productive value (NPV) mean uterine artery PI for prediction of preeclampsia.**

Test	Cutoff (Median)	Sensitivity	Specificity	PPV	NPV
uterine artery PI	0.98	61.2%	80.4%	79.0%	90.0%

**Receiver operating characteristic (ROC) analysis of uterine artery PI in preeclampsia patients.**

	Area	Std. error	Significant	95% Confidence Interval	
				Lower Bound	Upper Bound
Uterine artery PI	0.653	0.039	<0.001	0.577	0.730



**Figure 1:** Receiver operating characteristic (ROC) curve analysis of diagnosing of preeclampsia. Each receiver characteristic curve is expressed as a solid line. AUC: area under the curve.

II ( $p=0.028$ ). BMI is said to be a high- risk factor for development of preeclampsia. Present study results are supported by Negin Rezavand *et al.* (2017)<sup>21</sup> study in which regression analysis did not find maternal age, parity and gestational age to be significantly predicting

**Table 4: Gestation weeks, mode of termination, and type of delivery and details of outcome baby in between group I and group II.**

Gestation age (weeks)	Group I (n = 100)	Group II (n = 100)	p-Value
		<b>38.01±3.23</b>	
<b>Mode of Termination</b>			
LSCS	33 (33.0%)	34 (34.0%)	0.881
VD	67 (67.0%)	66 (66.0%)	
<b>Delivery</b>			
Induced labor	42 (42.0%)	34 (34.0%)	0.338
Spontaneous	58 (58.0%)	67 (67.0%)	
<b>Baby</b>			
Weight	2.52±0.43	2.36±0.62	0.033*
Sex M/F	45/55	47/53	0.887
NNU/ NICU	17 (17.0%)	27 (27.0%)	0.089

\*=Significant

Preeclampsia. However, they also found BMI (adjusted  $R^2 = 10.3\%$ ,  $P= 0.006$ ) as a significant predictor of preeclampsia as shown in present study. Sibai *et al.* (1997)<sup>22</sup> also in their study found that increased BMI was a strong predictor for development of Preeclampsia (incidence of 12.6 % of Preeclampsia in BMI more than 34 Kg/meter square.) Another study done by Andrade. *et al.* (2014),<sup>23</sup> in which there was difference in BMI in normotensive and preeclamptic group but this was not statistically significant, (normotensive pregnancy ( $22.76 \pm 4.39$ ) versus PE (mild PE  $26.14 \pm 4.95$  and severe PE  $24.35 \pm 3.08$ ) ( $p=0.09$ )). In the longitudinal study conducted by Calxito A.C. *et al.* (2014),<sup>24</sup> BMI was not found to be determining factor for prediction of preeclampsia ( $p = 0.278$ ). Also, they did not show maternal age and nulliparity to be determining factor for preeclampsia ( $p = 0.418$ ), ( $p=0.092$ ) respectively. Brando AHF *et al.* (2014)<sup>25</sup> also

did not find BMI to be predictor for preeclampsia however this may be due to very small number of patients in preeclampsia group ( $n=9$ ) than control group ( $n= 50$ ) ( $p= 0.32$ ). Both the group were comparable in terms of complications in current pregnancy like anemia, GDM, cholestasis, hypothyroidism, Rh negative except FGR which was significantly higher in group II (24 % Vs 7% ; $p<0.001$ ) than group I. Similar results were found in a study done by Barati M *et al.* (2014)<sup>26</sup> who found 17 cases (4.5%) of abnormal uterine artery Doppler results and 15 of them (88.2%) developed preeclampsia and four cases (23.5%) had neonates small for gestational age. In accordance to this Calxito A. C. *et al.* (2014)<sup>24</sup> also found significant difference in fetal weight in preeclamptic ( $2602\pm 623$  gram) and normotensive patient ( $3100\pm 288$  grams) ( $p<0.001$ ) but there are some studies like Takase *et al.*<sup>27</sup> who did not find difference in birth weight among normotensive and preeclampsia group ( $3281\pm 229$  and  $3290\pm 100$  gms respectively). Present study on comparing Uterine artery Doppler velocimetry in two groups it was found that uterine artery PI was statistically significant different in two groups. Group II had higher mean uterine artery PI as compared to Group I ( $1.11\pm 0.43$  and  $0.90\pm 0.40$ ,  $p<0.001$ ). Also, the mean S/D was significantly different in two groups ( $p<0.038$ ). The mean RI (Rt and Lt) of uterine artery showed a closed gap between two groups. 8 patients had bilateral end diastolic notch in group II (28 -34 weeks) while 3 patients of group I (< 28 weeks) had bilateral End diastolic notch in uterine artery. In accordance with present study. Brandao AHF *et al.* (2012)<sup>25</sup> also showed, higher uterine artery PI value in preeclampsia group than normotensive group. Also, they have compared uterine artery PI at early and late second trimester gestation and concluded to have significantly lower PI value in early second trimester in normal pregnancy. Barati M. *et al.* (2014)<sup>26</sup> observed that mean uterine artery PI > 1.45 at 16 – 22 weeks of gestation can predict preeclampsia with specificity of 95.5% (95% CI, 70-92%), a sensitivity of 79% (95% CI, 43-82%), a negative predictive value (NPV) of 98.9% (95% CI, 72-96%), and a positive predictive value (PPV) of 88.2% (95% CI, 68-98%). Torres C and Raynor B *et al.* (2005)<sup>28</sup> who studied the uterine artery score and adverse pregnancy outcomes in a low-risk population during the

second trimester had similar result. The uterine artery score assigned one point to each abnormal parameter (RI >0.57, PI >1.0, S/D ratio >2.6 and notching) for each uterine artery, ranging from 0 (normal findings in both uterine arteries) to 8 (all abnormal in both arteries). In predicting pre-eclampsia, the score of 5 or more had a specificity of 89.5%, a sensitivity of 25%, an NPV of 77%, and a PPV of 46%. The better specificity and NPV of uterine artery PI in this study can be explained by use of uterine artery score in second trimester. So uterine artery Doppler is better to be done in second trimester. In present study, by utilizing a cut -off point of >0.98 (median), the overall sensitivity of mean uterine artery PI for diagnosis of preeclampsia was 61.2%, specificity of 70.4%, PPV of 79% and NPV of 90.0%. Pearson's correlation coefficient of uterine artery PI was positively correlated with preeclampsia which means that preeclampsia patient had higher value of uterine artery PI than normotensive patients. Various studies done to evaluate uterine artery PI as significant predictor of PET are shown below

## CONCLUSION

Uterine artery doppler is a non-invasive test with high negative predictive value which should be used for prediction of preeclampsia in all pregnant patients.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Study	Study year	Gestational age	Mean Ut artery PI (cut off)	Sensitivity	Specificity	PPV	NPV
Torres C and Raynor B <i>et al.</i>	2005	Second trimester	>1.0 (ut score >5)	25%	89%	46.0%	77.2%
Barati <i>et al.</i>	2014	16-22 weeks	>1.45	79%	95.5%	88.2%	98.9%
Present study	2019	20 -40 weeks	>0.98	61.3%	80.4 %	79.0%	90.0%

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