ORIGINAL RESEARCH PAPER

Obstetrics & Gynaecology

ROLE OF UTERINE ARTERY DOPPLER VELOCIMETRY IN EARLY PREGNANCY TO PREDICT PRETERM LABOR – A PROSPECTIVE STUDY AT A TERTIARY CARE CENTRE IN NORTH INDIA

KEY WORDS: Uterine artery doppler, Preterm Labor, Pulsatibility index, Perinatal morbidity and mortality

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ABSTRACT

BACKGROUND The utility of 2nd trimester uterine artery doppler is justified as a predictive screening test and emerging as a sonographic marker in early pregnancy for preterm birth in developing countries because of the high prevalence of mortality and morbidity due to outcomes of abnormal placentation.**MATERIAL AND METHOD** The study was a single-center prospective cohort study done among 2050 pregnant patients between 11 – 27 weeks of gestation who visited the outpatient department for their routine antenatal check up as well as emergency labor room admissions at a tertiary referral centre in north India over a period of 2 years from December 2020 to December 2022. Out of 2050 antenatal patients, 370 patients went into early preterm labor, 510 into late preterm labor, 910 delievered at term. **RESULTS** The area under the ROC curve (AUROC) for Uterine Artery Pulsatibility Index in early trimester predicting Pre-Term vs Term delivery was 0.768 (95% CI: 0.697 - 0.839), thus demonstrating fair diagnostic performance and was statistically significant (p = <0.001). At a cutoff of Pulsatibility Index ≥1.63, it predicts Pre-Term Delivery with a sensitivity of 60%, and a specificity of 91%. The odds ratio (95% CI) for Pre-Term Labor when Pulsatibility Index is ≥1.63 was 14.99 (6.46-34.74) while the relative risk (95% CI) was 2.86 (2.16-3.87). **CONCLUSION** Furthur research studies should be done including multiple centres to evaluate the generalizability of multiparametric models in different resource settings, in addition to assessing the impact of screening on clinical outcomes.

INTRODUCTION

Preterm delivery constitutes a major burden of neonatal morbidity and mortality as the prognosis for preterm infants is influenced by gestational age at delivery, survival increasing from less than 10% at 23 weeks to more than 95% by 33 weeks[1]. Despite concerns about preventing premature birth, it is currently considered a global epidemic, leading to the birth of approximately 15 million premature babies worldwide, and is estimated to account for approximately 11% of all births worldwide [2].Several attempts are being made to improve prenatal care and to establish a risk stratification criterion in early pregnancy for predicting preterm labor by various biochemical and sonographic markers, however, accurate risk prediction for early diagnosis and prevention of prematurity related complications still remains a major challenge for researchers. The onset of preterm delivery is either spontaneous or medically indicated, mainly for causes such as severe pre-eclampsia and intrauterine growth restriction (IUGR). The maternal spiral artery, the major continuation of the uterine artery undergoes physiological trophoblastic invasion during pregnancy leading to loss of the musculoelastic properties and conversion to high pressure, low resistance uteroplacental arteries allowing an increased blood flow to the placenta and the fetus. This process commences in the first and ends in early second trimester [3]. Various researches have extensively studied that the development of pre-eclampsia and IUGR leading to preterm delivery are consequences of impaired trophoblastic invasion of the myometrial segment of the maternal spiral arteries, resulting in increased impedance flow in the uterine arteries

Second trimester USG Doppler is usually performed between 20th and 24th weeks of gestation, considering that the physiologic process of trophoblastic invasion would have been completed by this time. The impairment or complete absence of the physiological process is associated with increased vascular resistance and impedance to blood flow towards the placenta and fetus preceding the onset of the complications [4]. The outcomes of abnormal trophoblastic invasion is derived from studies on the uterine artery doppler indices, because the uterine artery flow reflects the sum of resistances of the placental bed and of the placental perfusion [5,6].

Several studies have investigated the potentials of late 1st trimester and second trimester uterine artery Doppler in predicting risk of preterm labor and establishing it as an independent routine screening method in early pregnancy. Increased pulsatility index (PI) at 20–24 weeks of gestation can identify, at a false-positive rate of 5%, about 75% of women who subsequently develop pre-eclampsia of sufficient severity to require delivery before 33 weeks[7,8].Thus, the utility of 2nd trimester uterine artery doppler is justified as a predictive screening test and emerging as a sonographic marker in early pregnancy for preterm birth in developing countries because of the high prevalence of mortality and morbidity due to outcomes of abnormal placentation. Although, some research studies do not agree with the idea of uterine artery doppler indices being emerging as a screening tool, because of the heterogeneity in aetiology of complications of impaired placentation.

MATERIAL AND METHOD

STUDY DESIGN AND SITE

The study was a single-centre prospective cohort study done among 2050 pregnant patients between 11-27 weeks of gestation who visited the outpatient department for their routine antenatal check-up as well as emergency labor room admissions at a tertiary referral centre in north India over a period of 2 years from December 2020 to December 2022. Out of 2050 antenatal patients, 370 patients went into early preterm labor, 510 into late preterm labor, 910 delievered at term, 70 were post term and 190 patients were lost to follow up(excluded from the study).As the hospital was a tertiary referral centre, most of the women attending antenatal OPD had pre-existing medical conditions or were at an increased risk for pregnancy complications.

INCLUSION AND EXCLUSION CRITERIA

Women with singleton pregnancy with gestational age between 11-27 weeks of gestation willing to participate were included in the study Pregnant women with multiple gestation, diagnosed cervical insufficiency, uterine malformations or fetal congenital abnormalities, placenta praevia, oligo/polyhydramnios, medical problems like chronic hypertension, anaemia, diabetes mellitus or medically indicated preterm delivery were excluded from the study.

DATA COLLECTION

All Patients were subjected to detailed history taking, general, systemic and obstetrical examination, routine blood and urine investigation and Obstetrical USG with color doppler.

The uterine artery Doppler velocimetry was done using a Voluson V730 Expert Doppler ultrasound machine (GE Healthcare Ultrasound, Milwaukee, WI, USA) 3.5 MHz abdominal probe by a single ultrasonographer.The UtAs were identified at the crossover with the external iliac artery by an abdominal approach (Figure 1). Quantitative assessments of the wave by pulsatility index (PI) was performed. Both arteries were sampled and three consecutive waveforms were evaluated. For cases with a laterally positioned placenta, the PI value obtained from the ipsilateral UtA while for centrally positioned placenta, the artery with the lowest PI was chosen to best represent the uteroplacental circulation. The uterine artery flow velocity waveform was obtained by placing the Doppler pulsed gate on the target vessel 1cm distal to the crossover point and the insonation angle adjusted to <0.0001. We used mean UtA PI (left + right PI divided by 2) as a measure of UtA resistance.We defined increased PI as >90th centile (P90) and >95th centile (P95).

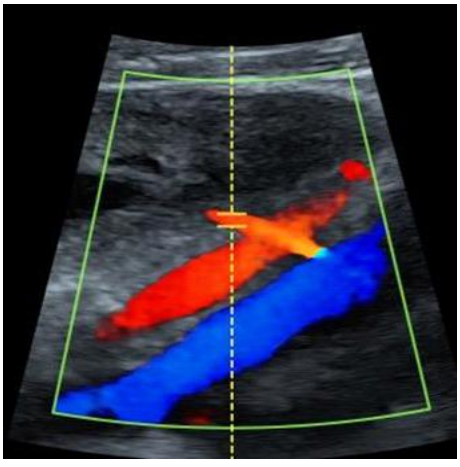

Figure 1 Doppler image of uterine artery at crossover iliac artery

OUTCOME MEASURES

All included women were followed until delivery. In our study, early preterm labor was defined as onset of labor between 28 – 34 weeks of gestation and late preterm labor was defined as onset of labor between 34 - 37 weeks of gestational age. Our primary outcome was spontaneous PTB before 37 weeks of gestation.

STASTICAL ANALYSIS

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures were coded, entered and analysed using Microsoft Excel software and imported into Statistical software SPSS version 20.0 for analysis. Qualitative result were represented as number and percentage while quantitative data were represented as mean ± SD. P value was set at <0.05 for significant results.

RESULTS

The study was a single-centre prospective cohort study done among 2050 pregnant patients between 14 – 27 weeks of gestation who visited the outpatient department for their routine antenatal check-up as well as emergency labor room admissions at a tertiary referral centre in north India over a period of 2 years from December 2020 to December 2022. Out of 2050 antenatal patients, 370 patients went into early preterm labor, 510 into late preterm labor and 910 delivered at term. 70 patients delivered post term and 190 patients were lost to follow up and thus were excluded from the study.

TABLE NO. 1 DISTRIBUTION OF THE PATIENTS ACCORDING TO SOCIODEMOGRAPHIC DATA

Age Group	No. Of Patients	Percentage
<20 Years	40	2.2%
20-25 Years	870	46.8%
26-30 Years	620	33.3%
>30 Years	330	17.7%
Mean±S.D		26.52±3.82
Gravida		
G1	200	10.8%
G2	580	31.2%
G3	620	33.3%
>G3	460	24.7%
Socio-Economic Status		
Lower	1090	58.6%
Lower-Middle	550	29.6%
Upper Middle	200	10.8%
Upper	20	1.07%
Education		
Illiterate	980	52.7%
Primary	470	25.3%
Higher Secondary	270	14.5%
Intermediate	110	5.9%
Graduate	30	1.6%
Residential Area		
Rural	1160	62.4%
Urban	700	37.6%
Substance Use		
None	1450	78.0%
Tobacco	190	10.2%
Cigarette	170	9.1%
Alcohol	50	2.7%
BMI		
<18.5 Kg/m2	350	18.8%
18.5-24.9 Kg/m2	770	41.4%
25.0-29.9 Kg/m2	450	24.2%
30.0-34.9 Kg/m2	290	15.6%
Mean ± S.D	23.84±4.47	

Table no. 1 shows that majority of the patients, 870 (46.8%) belonged to the age group between 20 – 25 years with a mean (SD) of 26.52 (3.82) years, median (IQR) was 26.00 (24-29) years and was not normally distributed (Shapiro-Wilk Test: p = <0.001). Also, maximum patients were 3rd gravida (n=460, 33.3%), belonged to lower class(n=1090, 58.6%) and were from rural background (n =116,62.4%).Majority of the patients (n=1450, 78%) gave no history of any addiction and had a BMI between 18.5 – 24.9kg/m^2 (n=770, 41.4%) with a mean (SD)(Kg/m2) of 23.84 (4.47) and median of 23.14 (20.62-26.86).The variable BMI (Kg/m2) was not normally distributed (Shapiro-Wilk Test: p = <0.001).

TABLE NO. 2: Distribution of the Patients According to Gestational Age at USG Color Doppler (Weeks)

Gestational Age at USG Color Doppler	No. Of Patients	Percentage
11 – 136 Weeks	533	28.65%
14 – 186 Weeks	297	15.96%

19 - 226 Weeks	610	32.79%
23 - 27 Weeks	420	22.58%
Total	1860	100.0%
Mean ± S.D	21.52 ± 6.46	

Table no 2 shows that majority of the patients were screened around 19 – 22 weeks(n= 610, 32.79%) when they reported for their Level II scan followed by 11 – 13 weeks (n= 533, 28.65%) when they had their 1st antenatal check-up and their NT – NB scan. The mean gestation age of screening was 21.52±6.46 weeks. The variable was not normally distributed (Shapiro-Wilk Test: p = <0.001).

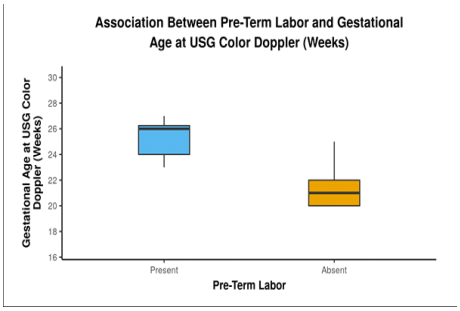

Figure 2: Box and Whisker plot of association between gestational age at USG Color Doppler and Preterm Labor

The mean (SD) of Gestational Age at USG Color Doppler (Weeks) in the Pre-Term group was 25.49 (1.33) while in the Term group was 21.40 (1.33). There was a significant difference between the 2 groups in terms of Gestational Age at USG Color Doppler (Weeks) (W = 7787.500, p = <0.001).

TABLE NO. 3: Distribution of Patients According to Uterine Artery Doppler Pulsatibility Index (n=179)

Pulsatibility Index	No. Of Patients	Percentage
<1.21	1200	67.0%
≥1.21	590	33.0%
Total	1790	100.0%
Mean ± S.D	1.55 ± 1.07	
P value	<0.001	

Table no. 3 shows that out of 1790 antenatal patients who delivered preterm or around term (70 patients who delivered post term were excluded), 120(67%) had uterine artery pulsatibilty index less than 1.21 while 59(33%) had uterine artery pulsatibilty index more than or equal to 1.21.

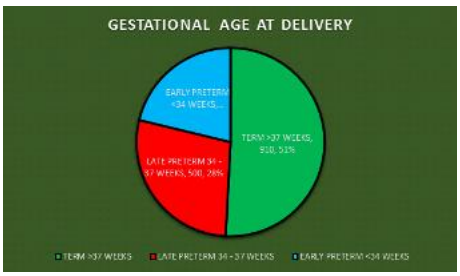

FIGURE 3: Distribution of the Patients According to Gestational Age at Delivery (n = 179)

*Patients who delivered beyond 40 weeks (n=70) and patients lost to follow up (n=190) were excluded from the study. Figure 3 shows that out of 1790 antenatal patients, 380(21.2%) patients went into preterm labor before 34 weeks , 50(27.9%) patients went into preterm labor between 34 – 37 weeks and 91(50.8%) patients were delivered at term.

TABLE NO. 4 Uterine artery PI as a marker for prediction of preterm vs term delivery

Parameter(Uterine artery pulsatibilty index) Preterm Vs Term	Value (95% CI)
Cutoff (p value)	≥ 1.63 (<0.001)
AUROC	0.768 (0.697 - 0.839)
Sensitivity	60.2% (49-71)
Specificity	91.2% (83-96)
Positive Predictive Value	86.9% (76-94)
Negative Predictive Value	70.3% (61-78)
Diagnostic Accuracy	76.0% (69-82)
Positive Likelihood Ratio	6.85 (3.46-13.57)
Negative Likelihood Ratio	0.44 (0.33-0.57)
Diagnostic Odds Ratio	15.71 (6.77-36.46)

The area under the ROC curve (AUROC) for Uterine Artery Pulsatibility Index in early trimester predicting Pre-Term vs Term delivery was 0.768 (95% CI: 0.697 - 0.839), thus demonstrating fair diagnostic performance and was statistically significant (p = <0.001). At a cutoff of Pulsatibility Index ≥1.63, it predicts Pre-Term Delivery with a sensitivity of 60%, and a specificity of 91%. The odds ratio (95% CI) for Pre-Term Labor when Pulsatibility Index is ≥1.63 was 14.99 (6.46-34.74) while the relative risk (95% CI) was 2.86 (2.16-3.87).

TABLE NO. 5 Uterine artery PI as a marker for prediction of early preterm vs late preterm delivery

Parameter(Uterine Artery Pulsatibility Index) Early Vs Late Preterm Labor	Value (95% CI)
Cutoff (p value)	≥ 1.72 (0.262)
AUROC	0.57 (0.447 - 0.693)
Sensitivity	60.5% (43-76)
Specificity	56.0% (41-70)
Positive Predictive Value	51.1% (36-66)
Negative Predictive Value	65.1% (49-79)
Diagnostic Accuracy	58.0% (47-68)
Positive Likelihood Ratio	1.38 (0.92-2.06)
Negative Likelihood Ratio	0.7 (0.44-1.12)
Diagnostic Odds Ratio	1.95 (0.83-4.6)

The area under the ROC curve (AUROC) for Pulsatibility Index predicting Early vs Late preterm labor was 0.57 (95% CI: 0.447 - 0.693), thus demonstrating poor diagnostic performance. It was not statistically significant (p = 0.262). At a cutoff of Pulsatibility Index ≥1.72, it predicts Early preterm labor with a sensitivity of 60%, and a specificity of 56%.

The odds ratio (95% CI) for Early preterm labor when Pulsatibility Index is ≥1.72 was 1.75 (0.75 - 4.1) while the relative risk (95% CI) for early preterm labor was 1.38 (0.85-2.27).

Table No. 6: Comparison of the Pre-Term Vs Term Group in Terms of Association with Pulsatibility Index

Pulsatibility Index	Pre-Term Labor		Wilcoxon-Mann-Whitney U Test	
	Present	Absent	W	p value
Mean (SD)	1.61 (0.26)	1.49 (1.48)	6150.500	<0.001
Median (IQR)	1.73 (1.39-1.83)	1.35 (1.25-1.46)		
Range	0.87 - 1.98	0.67 - 15.3		

The variable Pulsatibility Index was not normally distributed in preterm and term group. The mean (SD) of Pulsatibility Index in the Pre-Term group was 1.61 (0.26) while in Term group was 1.49 (1.48). The median (IQR) of Pulsatibility Index in the Pre-Term Labor group was 1.73 (1.39-1.83). The Pulsatibility Index in the Pre-Term group ranged from 0.87 - 1.98 while in the term group ranged from 0.67 – 1.53. There was a significant difference between the 2 groups in terms of Pulsatibility Index (W = 6150.500, p = <0.001).

DISCUSSION

This study attempted to establish Uterine artery PI as a marker for prediction of preterm labor in late 1st and 2nd

trimester of pregnancy and concluded that it has a fair diagnostic performance and was statistically significant (p = <0.001). At a cutoff of Pulsatibility Index ≥1.63, it predicts Pre-Term Delivery with a sensitivity of 60%, and a specificity of 91%.But, on the other hand the predictive ability to detect early vs late preterm labor demonstrated poor diagnostic performance,

A major strength of this study was that it had a larger sample size including women with both low-risk and high risk (due to the hospital being a tertiary referral center) for spontaneous PTB. The major limitation of the study was being a single tertiary centre study results might be influenced by the trends and protocols of inpatient admission of the hospital. Most of the antenatal patients visiting the hospital often have comorbidities or a complicated previous pregnancy. Furthermore, the centre has maximum no. of patients with a non-white ethnicity and low socio-economic status, both of which are known as risk factors for PTB [9].

A previous cohort study performed in the UK between 1999 – 2002 assessing the relation between second-trimester UtA Doppler and spontaneous PTB reported no significant correlation between the two [10]. Similar to our study, Fonseca et al [11] reported the relation between second-trimester UtA PI and spontaneous PTB showing that UtA PI was higher in women with spontaneous PTB before 33 weeks. Our results are also in agreement with Melchiorre et al who observed that first-trimester UtA-PI is predictive of preterm labor.Similarly, Poon et al [13] observed a strong association and similar predictive values when using mean UtA-PI in the first-trimester. Lefebvre et al [14] observed that first-trimester UtA-PI collected at the level of the internal cervical os correlated better with mid-trimester UtA-PI done at the level of the apparent crossover with the external ilia vessels. Also, the study correlates well with the meta-analysis of Velauthar et al [15] suggesting that first-trimester UtA-PI is highly associated with early preterm labor making it a useful tool in the early detection of women who could benefit from aspirin prophylaxis.

UtA Doppler measurement being a relatively quick and economical tool can be easily performed during the routine fetal 1st or 2nd trimester anomaly scan which is already included in the national screening program. The study concluded higher risk of spontaneous PTB in women with an abnormal UtA Doppler, strengthening the hypothesis that abnormal placentation has a relation with spontaneous PTB. Thus, further research should evaluate the possible role of antiplatelet therapy as a new strategy in the prevention of PTB [16 – 19]. Also, more prospective studies should be taken up to understand if abnormal UtA Doppler contributes to the multivariable etiology underlying spontaneous PTB.

Based on the findings of our study, we recommend that UtA-PI should be included in first-trimester models for the prediction of preterm labor but should be adjusted for gestational age (or CRL) at the time of measurement and combined with other markers (maternal characteristics and biochemical markers) to reach optimal benefits as it might result in drastic changes in the screening outcomes for prevention of perinatal morbidity and mortality.

CONCLUSION

UtA Doppler is gradually being recognised as an important sonographic marker in detection of (spontaneous) PTB. It may prove very beneficial in coming future in low resource settings and developing countries to reduce the burden of preterm delivery. Algorithms including maternal characteristics and biochemical markers with Doppler velocimetry in the first trimester have the potential of detection of over 90% at a false positive rate of 10%, thus, including them into risk calculation is mandatory. Further, more research studies should be done including multiple centres to evaluate the generalizability of multiparametric models in different resource settings, in addition to assessing the impact of screening on clinical outcomes.

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CONFLICT IF INTEREST – None declared

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