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The role of uterine artery Doppler in the prediction of pre-eclampsia at 13- to 16-week gestation

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ABSTRACT

Objective: Uterine artery Doppler flow assessment during early pregnancy can help in the prediction of pre-eclampsia. The present study aimed to assess the role of uterine artery Doppler ultrasound in early prediction of pre-eclampsia at 13-16 weeks of gestation.

Methodology: This observational study included 80 antenatal women, aged 16-35 years, with 13-16 weeks of gestational age with singleton pregnancy, from December 2017 - June 2019. Demographic data, medical history was collected. Doppler assessment of the uterine arteries was performed at 13-16, 24-26 weeks of gestation to record uterine artery diastolic notch (UADN) and uterine artery Doppler indices, viz, resistance index (RI) and pulsatility index (PI). Pregnancy events, delivery and neonatal outcome were noted during follow up. Statistical analysis was performed by using R software (Version 3.6.0).

Results: Prevalence rate of pre-eclampsia was 12.5%. At 12-16 weeks, UADN was seen in 35% cases with mean RI, PI of 0.62 and 0.96. At 24-26 weeks, it was noted in 15% of the study cases (RI: 0.53 and PI: 0.79). A significant (P<0.05) association was observed between UADN at 24-26 weeks and development of pre-eclampsia. At 13-16 weeks gestation, the specificity and positive predictive value (PPV) for UADN were 70.49 and 35.7%, respectively; whereas when UADN and RI were considered together, the specificity and PPV increased to 100%.

Conclusion: The uterine artery Doppler ultrasound effectively predicted the development of pre-eclampsia during early pregnancy (13 to 16 weeks gestation) screening.

Key words: Pre-eclampsia, Diastolic notch, Pulsatility index, Uterine artery, Resistance Index

INTRODUCTION

Pre-eclampsia (PE) continues to be one of the leading causes of maternal and perinatal morbidity and mortality, with an estimated 10-15% of all maternal deaths in pregnancy, globally. [1] Due to lack of any proven effective method for pre-eclampsia prevention, the focus of routine antenatal care has been on identifying women at risk and offering more intensive antenatal care. Therefore, the focus of current research has been on identifying patients at high risk for PE. At present, the first and second trimesters are the preferred gestational duration for screening of PE [2].

There is no single, reliable, and cost-effective screening test for the detection of PE. Earlier, the serum uric acid level was used as an indicator of PE, but it is now no longer used due to its lack of sensitivity and specificity as a diagnostic tool [3].

The assessment of PE by uterine artery Doppler (UAD) at 24-26 weeks of gestation has been associated with poor results and poor prediction of term PE (late-onset) [4]. Additionally, this delayed prediction led to delay in prevention mechanisms. For example, the use of low-dose aspirin was more effective when initiated before 16 weeks of gestation as compared to between 24-26 weeks of gestation, as it reduced the risk of severe PE [5].

The assessment of PE in early pregnancy (13-16 weeks) is essential for developing early prevention mechanisms. Thus, UAD which is a noninvasive method for assessing the uteroplacental circulation in early pregnancy (13-16 weeks) is becoming an essential tool [6]. Furthermore, a high pulsatility index (PI) and resistance index (RI) along with persistent uterine artery notching in UAD wave form are the best screening tests for PE and are used in the assessment of uteroplacental blood flow in UAD [7].

UAD could also be regarded as an adjunct screening tool for intrauterine growth restriction (IUGR). This fetal growth restriction is often associated with PE and is an important cause of perinatal morbidity and mortality [8]. Its abnormal results have been strongly associated with several types of adverse perinatal and maternal outcomes such as intrapartum and antepartum fetal distress, metabolic and neurodevelopmental diseases in late infancy till adulthood, etc[9].

Studies investigating the predictive accuracy of UAD indices have revealed considerably varied results [10, 11], raising questions on its applicability as a predictive test. Thus, the purpose of this study was to assess the predictive value of UAD in early pregnancy (at 13-16 weeks of gestation) for the prediction of PE and subsequent perinatal outcome.

MATERIALS AND METHODS

Study design

With the institutional ethics committee's approval **(Approval no.- KIMSDU/IEC-307/030/4/07/2017)**, this single-centered, hospital-based, prospective, observational study was conducted in the Department of Obstetrics and Gynecology at a private medical college in Karad (Maharashtra) over a period of 19 months (December 2017 - June 2019). Informed consent was obtained from all the patients included in the study. To show a small difference statistically significant, we had to choose a small effect size (Cohen's d). For an effect size of w=0.4 (medium), significance level of 95%, and power of 90%, the sample size was ~66 for Chi-square test of independence with df 2 (3-1 * 2-1).

Selection criteria

Eighty pregnant women aged between 16 and 35 years and at 13 to 16 weeks of gestation with singleton pregnancy were included in the study. Patients with multiple gestations, congenital anomaly of fetus, chronic hypertension, renal disease, or cardiac disease were excluded from the study.

Data collection

Data regarding age, educational and social status, medical history, and family history of PE was collected by interviewing the patients before the procedure.

Uterine artery Doppler assessment

Doppler assessment of the uterine arteries was performed to assess the presence of uterine artery diastolic notch (UADN) and UAD indices (RI [normal range: 0.50-0.70] and PI [normal range: 0.48-0.67]) values on two occasions, the first between 13-16 weeks and the second between 24-26 weeks of gestation. Increased resistance to flow in the uterine artery was associated with the appearance of diastolic notch and increase in all UAD indices. The equipment used was Siemens Acuson x300 USG machine with 5-megahertz transabdominal curvilinear transducer and a Doppler carrier frequency of 2.5-megahertz. Routine fetal biometric measurements were obtained followed by color Doppler examination of the uterine arteries.

These patients were followed up until delivery and the details of pregnancy events and delivery and neonatal outcomes were noted. The abnormal pregnancy outcome considered was PE; and perinatal outcomes were intrauterine fetal demise (IUFD), Apgar at 5 min, birth weight, and NICU admission.

Statistical analysis

Statistical analysis was performed by using R software (Version. 3.6.0). Data was recorded in Microsoft excel and expressed as mean ± standard deviation along with frequency and percentage. Qualitative variables were analyzed using Chi-squaretest of independence and paired *t*-test for continuous variables. The performance of the diagnostic method was evaluated by calculating sensitivity, specificity, positive and negative predictive values, and likelihood ratios for abnormal {sensitivity/(1-specificity)} and normal tests {(1- sensitivity)/specificity} at 95% confidence interval. Data was considered statistically significant when $P \leq 0.05$.

RESULTS

The present prospective study was carried out in 80 pregnant women (study cases). Table 1 presents the demographic, baseline, and clinical variables data of all the patients.

In this study, majority (52.5%) of the women were ≤20 years old, which stipulates that most of them were under-aged and medically not fit for a healthy pregnancy. Most (61.25%) of them had a poor educational status as they had only secondary-level education (5^{th}-10^{th} class). Their socioeconomic status showed most of them to either belong to class III (40%) or class II (32.5%) (Table 1).

Majority (76.25%) of the women had systolic BP <140 mmHg and diastolic BP <90 mmHg, stipulating that most of them had their BP in the normal range. Furthermore, majority of the women had their first scan at a mean gestational age of 16 weeks and the second scan at 29 weeks (Table1).

UADN was seen in 35% of the cases at 12-16 weeks and in 15% of them at 24-26 weeks. Also, 20% of the study cases who had UADN at 12-16 weeks showed no UADN at 24-26 weeks and did not develop hypertension. Women with persistence of UADN into the 2nd trimester had increased risk of developing PE.

The mean RI1 and PI1 for all study cases at 12-16 weeks scan was 0.65±0.05 and 0.96± 0.06, respectively. Similarly, at 24-26 weeks, the mean RI2 and PI2 was 0.57± 0.07 and 0.63± 0.13, respectively, for all study cases.

No significant association was observed between UADN at 13-16 weeks with development of Pre-eclampsia ($P>0.05$). However, a significant association was observed between UADN at 24-26 weeks with development of Pre-eclampsia ($P<0.05$) (Table 2). The odds of development of PE was 30.47 times more in the study cases with UADN at 24-26 weeks than those without (OR [95% CI]: 30.47 [5.34- 327.57]).

The mean RI at 12-16 weeks and at 24-26 weeks for pre-eclamptic women was statistically significant ($P<0.05$) as compared to the non-pre-eclamptic women, respectively. This stipulates that in women who subsequently developed PE, the mean RI was higher than in those who did not (Table 3).

The mean PI at 12-16 weeks and 24-26 weeks for pre-eclamptic women was statistically significant ($P<0.05$) as compared to the non-pre-eclamptic women, respectively. This stipulates that in women who subsequently developed PE, the mean PI was higher compared to those who did not (Table 3).

A significant association between RI at 13-16 weeks of gestation and pre-eclamptic status in women was observed in the presence of UAD notching at 13-16 weeks gestation ($P=0.00$), stipulating the combined effectiveness of RI and UAD notching in predicting the pre-eclamptic status of pregnant women (Table 3).

At 13-16 weeks, the specificity and PPV for UADN was found to be 70.49% and 35.7%, respectively. When UADN and RI were considered together, the specificity and PPV increased to 100% while the NPV remained constant (Table 4).

While determining the perinatal outcomes of study cases, it was observed that the mean gestational age at delivery was 38+1 week, 75% had full-term vaginal delivery, 10% had preterm vaginal delivery, and 15% had cesarean delivery. The mean birth weight was 2.84 Kg; mean Apgar at 1 min and 5 min was 7 and 8, respectively. In pre-eclamptic women, 3 babies were associated with IUGR with no IUFD. Mean duration of NICU stay was 4 days (Table 5).

DISCUSSION

The present prospective study was carried out to assess whether UAD at 13-16 gestation weeks can be used as an effective screening test to predict the development of PE. Data from the UAD assessment for presence of UADN, RI, PI values, both at 13-16 and 24-26 weeks formed the basis of the study.

Majority of the women were aged ≤20 years with poor educational and socio-economic status in this study. This is contrast to the study conducted by Papageorghiou et al [12] in which most of the patients were in the age group of 25-30 years with average/good educational and socio-economic status. This difference could be due to different ethnic and geographical backgrounds as in India, early marriage of girls (especially with poor educational and socio-economic status] is still in practice.

Most of the women in this study had a mean gestational age of 16 weeks during their first scan and 29 weeks during the second scan. This is in accordance with a previously published study in which the mean gestational age of pregnant women was 15 and 30 weeks during the first and second scan, respectively. This stipulates that the scan process usually initiates from second trimester [13].

Out of the 80 pregnant women in this study, 10 developed PE indicating 12.5% prevalence rate. Similar findings were observed by Gupte et al (9-10%) [14]. However, this is in contrast with a study conducted by Shashi et al [15] that showed 20% prevalence rate for PE. This difference could be since the comparative study was carried out with a larger sample size and the study cases were from a rural background as compared to our study. Usually, women from a rural background visit the hospital when have some complications or when they are at high risk.

Previous literature indicates an association between RI and the development of PE before and after 37 weeks of gestation, designated as early and late PE. Greater RI was observed in patients who developed PE in the early trimester of gestation as compared to healthy patients [16]. Similar findings were noted in the present study as the RI in pre-eclamptic women was higher as compared to normal pregnant women at both 13-16 and 24-26 weeks of gestation. However, no difference was observed between the RI in normal and pre-eclamptic pregnant women in a study conducted by Da Costa et al [17].

Trophoblastic invasion of the spiral arteries is impaired in complicated pregnancies due to PE. This failure of invasion results in higher placental resistance, which further shows altered blood flow pattern in Doppler ultrasound. Consequently, in the first and second trimester of pregnancy, the PI in the uterine arteries is increased. This increased PI is associated with a higher risk of PE as an adverse pregnancy outcome [18]. Our study agrees with this observation as the mean PI at 12-16 weeks and at 24-26 weeks of gestation for pre-eclamptic women was significantly high as compared to the non-pre-eclamptic women, which is further in agreement with the findings reported by Da Costa et al [17].

This study further confirmed the high NPV (82.69%) and RI of the UADN, which is consistent with previous studies [19], indicating that PE is unlikely to occur if the UAD waveform is normal. To avoid unnecessary intensive surveillance and intervention, the clinical utility of UAD screening depends on the negative predictive value suggesting that patients with a negative screening test truly do not have the disease [20].

The usual issue with UAD ultrasound as PE screening test is the relatively low PPV of abnormal waveforms as observed in the previous studies. The PPV for predicting PE ranged from 7-31% [21, 6]. Similar observation was made in our study, as the PPV was 35.71% for prediction of PE by UADN alone. However, the association of UADN with RI gave 100% PPV, which is a significant finding in our study.

Additionally, the sensitivity of UADN in the present study was 52.63% for prediction of PE, which is lower than the values observed in previous studies.[20] Similar was the case with specificity, as specificity of UADN was high (70.49%) as compared to previous studies [21]. These differences could be due to the lower cut-off value of mean RI in our study.

The mean gestational age at delivery was 38+1 week and 10% had preterm vaginal delivery. About 10% babies were delivered pre-term, and the mean birth weight was 3.6 Kg. In pre-eclamptic women, 15.79% babies were associated with IUGR and IUFD in one pre-eclamptic woman. This is in accordance with a study conducted by Geipel et al in which the mean gestational age at delivery was 36 weeks, 9% had preterm vaginal delivery, 9% babies were born preterm, and mean birth weight was 2.38 Kg [22]. This highlights the effectiveness of UAD ultrasound in predicting PE and resultant maternal and neonatal outcomes.

Our study has its own limitations. First, the sample size included only low-risk pregnant women. Second, prediction of PE by UAD screening in combination with PI was not performed. Third, management strategy for treatment of PE has not been explored. Future studies are recommended to measure the uterine artery waveform in high-risk patients to increase the sensitivity for detection of PE and to explore pharmacologic treatment or management strategies for preventing it.

CONCLUSION

Women with an abnormal UAD and increased PI and RI values at 13-16 and 24-26 weeks of gestation have a considerably higher risk for developing PE. On the contrary, women with normal UAD are unlikely to develop PE. Therefore, UAD could be useful in the early detection of PE and in avoiding unnecessary interventions and intensive surveillance.

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TABLES:

Table 1: Distribution of demographic, baseline, and clinical variables

Demographic variables	**Frequency n (%) [a]**
Age groups (years)	
≤20	42 (52.5)
21-25	27 (33.75)
26-30	9 (11.25)
>30	2 (2.5)
Total	**80 (100)**
Educational status (in grades)	
Primary (1-4)	1 (1.25)
Secondary (5-10)	49 (61.25)
Higher Secondary (11-12)	29 (36.25)
Graduate	1 (1.25)
Total	**80 (100)**
Socioeconomic status (in class) [b]	
2	2 (2.5)
3	32 (40)
4	26 (32.5)
5	20 (25)
Total	**80 (100)**
Clinical variables in third trimester	
Systolic BP[c] (mmHg)	
<140	61 (76.25)
≥140	19 (23.75)
Total	**80 (100)**
Diastolic BP (mmHg)	
<90	61 (76.25)
≥90	19 (23.75)
Total	**80 (100)**
Gestational age at scan (in weeks) (Mean ± SD) [d]	
GA1[e]	16 ± 0.85
GA2[f]	29 ± 0.56

a: Percentage; b: As per modified B.G. Prasad classification of socioeconomic status (Prasad, 1970); c: Blood pressure; d: Standard deviation; e: Gestational age at 1st scan; f: Gestational age at 2nd scan

Table 2: Association of uterine artery diastolic notch (UADN) with development of pre-eclampsia

UADN at 13-16 week	**Pre-eclampsia**		***P*value[a]**
	Present N (%)	**Absent N (%)**	
Present (n=28)	10 (35.71)	18 (64.29)	0.116
Absent (n=52)	9 (17.30)	43 (82.70)	
UADN at 24-26 weeks			
Present (n=12)	10 (83.33)	2 (16.67)	0.000
Absent (n=68)	9 (13.23)	59 (86.77)	

a: Chi-square test of independence; N (%): Number (percentage)

Table 3: Correlation between resistance index and pulsatility index at 13-16 weeks and 24-26 weeks of gestation (UAD) in pre-eclamptic and normal study cases

Gestational age (weeks)		**Resistance Index (RI) (Mean ± SD)**	***P* value [a]**
At 13-16 (RI1)	Pre-eclamptic women (n=10)	0.62±0.06	0.004
	Normal pregnant women (n=18)	0.58±0.03	
At 24-26 (RI2)	Pre-eclamptic women (n=10)	0.53 ± 0.10	0.001
	Normal pregnant women (n=2)	0.45 ± 0.05	
At 13-16 (PI1)	Pre-eclamptic women (n=10)	0.96 ± 0.09	$6.74e^{-06}$
	Normal pregnant women (n=18)	0.89 ± 0.02	
At 24-26 (PI2)	Pre-eclamptic women (n=10)	0.79 ± 0.21	$1.551e-^{08}$
	Normal pregnant women (n=2)	0.6±0	

A: Mann-Whitney U test; SD: Standard deviation; RI1: Resistance Index at 13-16 weeks; RI2: Resistance Index at 24-26 weeks; PI1: Pulsatility Index at 13-16 weeks; PI2: Pulsatility Index at 24-26 weeks

Table 4: Prediction of pre-eclampsia at 13-16 weeks by uterine artery Doppler screening

Diagnostic variable	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Positive LR (95% CI)**	**Negative LR (95% CI)**
UADN	52.63	70.49	35.71	82.69	1.78 (1.00, 3.17)	0.67 (0.41, 1.11)
UADN and RI =0.7	40.00	100	100	82.69	-	0.60 (0.40, 0.91)

UADN: Uterine artery diastolic notch; LR: Likelihood Ratio; PPV: Positive Predictive Value; NPV: Negative Predictive Value; RI: Resistance Index

Table 5: Maternal and neonatal outcomes

Maternal outcomes	
Gestation age at delivery in pre-eclamptic women (weeks)	**Frequency (%) (n=19)**
>38	2 (10.53)
36-38	12 (63.16)
34-36	4 (21.05)
32-34	1 (5.26)
Mode of delivery (n=80)	
FTND	60 (75)
PTVD	8 (10)
LSCS	12 (15)
Total neonatal outcome (n=80)	
Variable	**Mean ± SD**
Birth weight (kg)	2.84±0.48

Apgar 1	7.81±0.59
Apgar 5	8.83±0.4
NICU Stay in days	4.1±4.51

F (%): Frequency (percentage); FTND- Full term normal delivery; PTVD: Pre-Term Vaginal Delivery; LSCS: lower (uterine) segment Caesarean section; NICU: Neonatal intensive care unit; Apgar: Appearance, Pulse, Grimace, Activity, and Respiration