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Original Research Article

Maternal pregnancy associated plasma protein-A (PAPP-A) and uterine artery Doppler changes as predictors of pre-eclampsia: a prospective observational study from a teaching hospital in Mysore, Karnataka, India

Sharanya Satish^{1*}, K. B. Suma¹, Madhu B.², Sujatha M. S.¹

¹Department of Obstetrics and Gynecology, ²Department of Community Medicine, JSS Medical College, JSS Academy of Higher Education and Research (deemed to be University), Mysore, Karnataka, India

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***Correspondence:**

Dr. Sharanya Satish,

E-mail: sharanyasatish15@gmail.com

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ABSTRACT

Background: Hypertensive disorder affects 10-12% of pregnancies. Identifying women, who are at risk is conducive to prompt gestational management. PAPP-A is a protein complex produced by the developing trophoblasts. Low levels of PAPP-A at 10–14 weeks is a marker of impaired placentation and a smaller placental mass. Doppler imaging permits non-invasive evaluation of the uteroplacental circulation and is invaluable in the management of high-risk pregnancies. The uterine artery Doppler screening identifies patients at risk for developing preeclampsia. To study the association of PAPP-A and the uterine artery Doppler changes as predictor of pre-eclampsia in pregnant women at 11-14 weeks of gestation.

Methods: This was a prospective study of 150 pregnant women presenting at 11-14 weeks of gestation for a prenatal check-up. After considering the inclusion and exclusion criteria, serum samples for PAPP-A were assayed. Ultrasound Doppler was used to obtain uterine artery flow velocity waveforms and mean pulsatility index and resistance index of uterine arteries were calculated. Cases were followed up till term and observed for development of pre-eclampsia.

Results: 48.6% had low serum PAPP-A levels, in which 77% developed PE. The Mean PI and RI is 2.34 ± 1.16 and 0.58 ± 0.1 respectively. 30% women with abnormal PI values and 24% of women with abnormal RI values developed PE.

Conclusions: The combination of maternal history with low serum PAPP-A levels and abnormal uterine artery Doppler at 11-14 weeks can be used as predictor of pre-eclampsia.

Keywords: High risk pregnancy, Uterine artery Doppler, Uteroplacental circulation

INTRODUCTION

Hypertensive disorders in pregnancy is one of the most common complication in pregnancy and it affects up to 10-12% of pregnancies.¹ It is one of the leading causes of maternal morbidity and mortality and cause of IUGR and low birth weight babies.^{2,3} So prevention of hypertensive

disorders could have salutary effects on pregnancy outcome for both the mother and child. 13% of the maternal deaths are in the women with preeclampsia and eclampsia that accounts for major cause of death.⁴ The maternal mortality and morbidity can be reduced by timely diagnosing and effective treatment, by reducing complications like eclampsia and HELLP syndrome.

Hence it is necessary to design a screening technique which is a reliable and cost effective for predicting preeclampsia in advance and thereby to bring down the incidence of maternal and fetal mortality and morbidity drastically. The factors that have been postulated to influence the risk of pre-eclampsia among the mothers include Diabetes, Obesity, Multiple pregnancy, Primigravida, Age above 30 years, Previous history of pre-eclampsia, Family history of hypertension, Chronic hypertension. The development of pre-eclampsia is a consequence of impaired trophoblastic invasion to maternal spiral arteries and it converts the narrow muscular vessels into wide non-muscular channels.⁴

The physiological process of trophoblastic invasion is reflected in the observation from Doppler ultrasound studies that impedance to flow in the uterine artery decreases between 6 weeks and 24 weeks of gestation and remains constant thereafter.⁵ Abnormal uterine artery Doppler artery waveforms reflect increased impedance in uterine circulation.⁶ The increased impedance is thought to occur secondarily to failure of trophoblastic invasion of spiral arteries.^{7,8} This concept has led to the idea of using doppler assessment of uterine artery flow velocity waveform as a screening test for predicting the risk of preeclampsia and its severity before onset of clinical manifestations. Presence of high impedance flow and abnormal doppler indices in the uterine arteries constitute an indirect evidence of abnormal placentation. In high proportion of pregnancies destined to develop preeclampsia the uterine artery pulsatility index is increased at 11 to 13 weeks.^{9,10} A high Resistance Index, Pulsatility Index and persistent uterine artery notching in uterine artery Doppler wave form has shown as the best screening test.

Thus, the Doppler assessment of uterine artery flow velocity waveform can be used as a screening test for predicting the risk of preeclampsia and its severity before onset of clinical manifestations. Low levels of PAPP-A at 10-14 weeks may be a marker of impaired placentation and a smaller placental mass.¹¹

The expression and secretion of PAPP-A increase during differentiation of villous cytotrophoblasts to syncytiotrophoblasts.¹² The paracrine effects of insulin-like growth factors (IGF) are thought to control the invasion of trophoblasts into the decidua. As PAPP-A is a protease for IGF binding proteins (IGFBP), low PAPP-A is associated with high levels of IGFBP. IGF is known to influence fetal growth by controlling uptake of amino acids and glucose as well as having an autocrine and paracrine role in trophoblast invasion.¹³⁻¹⁵

This consequently results in a lowering of free IGF, leading to impaired invasion of the trophoblasts into the maternal decidua. This hypothesis provides biologic plausibility for the association of low first trimester PAPP-A and the development of pre-eclampsia later in pregnancy.¹⁶

METHODS

This was a prospective observational study conducted at a tertiary care referral hospital in South India from January 2017 to July 2018.

Inclusion criteria

- All pregnant women at 11-14 weeks of gestation were enrolled into the study.

Exclusion criteria

- Chronic hypertension
- Twin pregnancy
- Molar pregnancy
- Chromosomal abnormalities of fetus,
- Comorbid conditions (DM, renal, cardiovascular and thyroid disorders).

The maternal factors taken into account were age, parity, BMI, socioeconomic status, past history of pre-eclampsia and family history of pre-eclampsia.

Sample size was calculated using formula $4pq/e^2$ where p is prevalence (proportion) of women with hypertensive disorder and also taking drop outs into consideration.

As per Williams obstetrics 24th edition about 5-10% of all pregnancies are complicated by hypertensive disorders. Hence with reference to literature p value taken as 10 hence.

- $p = 10$
- $q = 100 - p = 90$
- $e = \text{absolute error} = 5$ and $e^2 = 25$
- Hence sample size = $4 \times 10 \times 90 / 25 = 144$ approx. 150.

All pregnant women with confirmed pregnancy of 11-14 weeks of gestation visiting OBG OPD for regular antenatal care and fulfilling exclusion and inclusion criteria were interviewed to obtain detailed socio-demographic and clinical details. After thorough general, physical, systemic and obstetrical examination, consent profoma prepared and validated by expert group was given to the subjects and their valid consent was obtained for the test. Venous blood samples was obtained from subjects and centrifuged for ten minutes at 4 degree centigrade. Serum is separated and stored at -20 degree Celsius until analysis. Serum levels of PAPP A was measured by ELISA method. Uterine artery Doppler was done and mean pulsatility index and RI of right and left uterine artery was calculated. The patients will be followed up till term for development of pre-eclampsia

Statistical analysis

Categorical and continuous variables are expressed as numbers (percentage) and mean \pm standard deviation respectively. Chi square was applied to compare

categorical variables and student's t test was used to compare parametric continuous variables.

RESULTS

150 antenatal women with 11-14 weeks of gestation were selected for the study and were subjected for screening of serum PAPP-A and uterine artery Doppler ultrasound.

They are all followed up clinically till term for development of preeclampsia (Table 1).

Table 1: Baseline maternal characteristics clinically.

Characteristics	Primigravida	Multigravida
Numbers	79 (53%)	71 (47%)
Mean age (years)	25±4.8	28±3.88
Mean bmi (kg/m ²)	23±2.06	23±2.12
Socioeconomic status		
Lower	65 (82.3%)	62 (87.3%)
Lower middle	6 (7.6%)	3 (4.2%)
Upper middle	8 (10.1%)	6 (8.5%)
H/o pre-eclampsia		
Absent		53 (74.6%)
Present		18 (25.4%)
Family h/o pre-eclampsia		
Absent	60 (76.9%)	51 (70.4%)
Present	19 (23.1%)	20 (29.6%)

48.6% of study population had low or abnormal serum PAPP-A values and out of them 77% developed PE, low serum PAPP-A had statistically significant relation with development of PE, p value being 0.000 (Table 2).

Table 2: Abnormal PAPP-A levels in occurrence of pre-eclampsia.

PAPP-A		Pre-eclampsia		Total	P value
		Yes	No		
PAPP-A	Abnormal	54 (65.1)	16 (26.2)	70 (48.6)	0.000
	Normal	29 (34.9)	45 (73.8)	74 (51.4)	
Total		83 (100)	61 (100)	144 (100)	

48 (33.3%) of study population had abnormal RI values out of whom 35 (72%) of them developed PE which is statistically significant p value being 0.009 (Table 3).

Table 3: Comparison of abnormal 1st trimester uterine artery resistance index with pre-eclampsia.

RI value	Pre-eclampsia		Total	P Value
	Yes	No		
Normal	48 (57.8)	48 (78.7)	96	0.009
Abnormal	35 (42.2)	13 (21.3)	48 (33.3)	
Total	83 (100)	61 (100)	144 (100)	

56 (38.9%) of study population had abnormal PI values, 55 (98%) developed PE and it is statistically significant p value being 0.0001 (Table 4).

Table 4: Comparison of abnormal 1st trimester uterine artery pulsatility index with pre-eclampsia.

PI value	Pre-eclampsia		Total	p-value
	Yes	No		
Normal	28 (33.7)	60 (98.4)	88 (61.1)	0.000
Abnormal	55 (66.3)	1 (1.6)	56 (38.9)	
Total	83 (100)	61 (100)	144 (100)	

DISCUSSION

In the study, 150 women attending the outpatient department for antenatal care were analyzed for serum PAPP-A and Doppler changes of uterine artery at 11-14 weeks by transabdominal ultrasound. These patients were followed up till delivery and details of pregnancy events, delivery and neonatal outcome were noted. Out of 150 women, 6 women dropped out of study due to loss of follow up, hence 144 women were studied and 24% of them developed pre-eclampsia, incidence of which is more compared to the study conducted by Balci S et al in which 158 women were enrolled into the study and 10.75% of them had at least one poor pregnancy outcome.¹⁶ Serum PAPP-A levels were assessed between 11-14 weeks. As depicted in Table 2, out of 144 women included in the study, 70 women i.e., 48.6% of the study population had low PAPP-A values which is less than 1.13 Miu/ml, which is statistically significant as compared to non pre eclamptic group (p<0.000). Out of these 70 women (48.6%), 54 (77%) developed preeclampsia. 74 among study population had normal PAAPP-A value and 29 among them developed pre-eclampsia which showed that first trimester PAPP-A values are less in women destined to develop pre-eclampsia.

The sensitivities and specificities of first trimester PAPP-A for the prediction of preeclampsia was 82.4% and 29.8%, respectively in the study conducted by Balci S et al sensitivity being similar to present study which is 77% and the specificity being less i.e., 60%.¹⁶ Similarly, Sensitivity of 79% and specificity of 34% was noted in a study conducted by Burak Asiltas et al for PAPP-A as pre-eclampsia predictor. Positive predictive value (PPV) of present study was 65% and negative predictive value (NPV) was 73%.¹⁷ In a similar study conducted by Katherine R et al the sensitivity and specificity of first trimester PAPP-A in prediction of pre-eclampsia was 36.4% and 86.8%.^{17,18} Uterine artery Doppler assessment for abnormal RI, PI values, was done at 11-13 weeks. As depicted in Table 3 and Table 4, out of 144 women studied, 24% women with abnormal RI values and 30% of women with abnormal PI values developed preeclampsia. Mean PI in present study was 2.34±1.16 at 11-14 weeks.

As per Table 4, 88 of study population had normal PI, among whom 28 developed pre-eclampsia and 56 had abnormal PI values and 55 among them developed pre-eclampsia which is statistically significant ($p < 0.000$) as compared to non-preeclamptic women. As per the study by AM Martin et al uterine artery mean PI was 2.35 and its sensitivity in prediction of preeclampsia was 27%. Sensitivity and specificity of uterine artery PI in present study was 98% and 31% and NPV and PPV is 98% and 66%.¹⁹

In preeclamptic women in present study mean RI at 11-14 weeks is 0.58 ± 0.1 . As shown in Table 3, 96 among study population had normal RI value, 48 among them developed pre-eclampsia and 48 of study population had abnormal RI value and 35 among them developed pre-eclampsia hence it has statistically significant relation as compared to non-preeclamptic group ($p < 0.009$) and hence may help in prediction of preeclampsia. Sensitivity and specificity of uterine artery RI is 80% and 50% and NPV and PPV is 78% and 53% respectively. Mean gestation age at delivery is 36 weeks, 52% had full term vaginal delivery and 9.3% had preterm vaginal delivery and 38.7% had Caesarean delivery. In preeclamptic women, 7 babies were associated with IUGR, IUFD in 2 preeclamptic woman and 33.3% babies of preeclampsia women required NICU admission. Mean duration of NICU stay is 15 days. Kevin S et al concluded that in the pregnancies resulting in preeclampsia, the median PAPP-A was lower, and the median uterine artery mean PI was higher. The detection rate for a 5% false positive rate was 14.1% for PAPP-A, 54.7% for uterine artery mean PI and 62.1% for a combination of PAPP-A and uterine artery mean PI.²⁰

Authors found increased first trimester uterine artery PI and maternal history of hypertension/pre-eclampsia and low first trimester PAPP-A level to be risk factors for pre-eclampsia. Combined uterine artery Doppler and PAPP-A achieved better detection rates than either of them alone and the difference was close to statistical significance. Our results suggest that uterine artery Doppler examination is useful in predicting pre-eclampsia from as early as the first trimester. The role of PAPP-A in the prediction of pre-eclampsia is as important as is abnormal Doppler in the prediction of PE. These observations may reflect the different pathophysiological mechanisms involved in pre-eclampsia and SGA, with abnormal Doppler reflecting the inadequate trophoblastic invasion of the maternal spiral arteries and low PAPP-A values the inherent inability of the placenta to support the full growth potential of the fetus. This study has the limitation of being a single center study with a small sample size. Further large sample size study would be required to prove the association between the markers and preeclampsia.

Pathophysiological changes in pre-eclampsia are believed to occur in early pregnancy and antedate clinical

manifestation of the disease. An ideal screening test should be simple, inexpensive, reproducible, widely and easily used, non-invasive and carried out in early pregnancy to allow for more efficient preventive or therapeutic intervention. At the time of 11–14-week ultrasound examination of uterine artery Doppler in combination with PAPP-A can provide an early assessment of risk for uteroplacental insufficiency. New technology ultrasound machines almost invariably offer color Doppler modalities and trained sonographers would require little additional time to examine the uterine arteries at no additional cost.

CONCLUSION

From present study authors conclude that Serum PAPP-A at 11-14 weeks of gestation was low in patients at risk of Pre-eclampsia. Uterine artery Doppler done in women with 11-14 weeks of gestation showed elevated Resistance index and Pulsatility index in women at risk of Pre-eclampsia. First trimester serum PAPP-A and the uterine artery Doppler changes can be used as predictors of pre-eclampsia. Routine use of first trimester serum PAPP-A and uterine artery Doppler is recommended for early prediction of pre-eclampsia.

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