Original Research Article

Early trimesterprediction of hypertensive disorders in pregnancy using pregnancy associated plasma protein A

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ABSTRACT

Background: The prediction of hypertension in first trimester is fairly a new concept in recent years , studies combining various parameters in the first trimester of pregnancy have been undertaken but an combination with high predictive value is to be developed. The objective of this study is to predict preeclampsia in first trimester using pregnancy associated plasma protein A.

Methods: A prospective cohort study was done at the department of obstetrics and gynaecology JJM medical college, Davangere, Karnataka with pregnant women attending the antenatal OPD at 11-14 weeks of gestation. A pre-formed questionnaire was filled for the enrolled women then blood pressure was recorded, pregnancy associated plasma protein A (PAPPA) done at 11-14 weeks of pregnancy. IBM SPSS version 22 for windows was used for statistical analysis of data.

Results: Low PAPPA itself is not a strong indicator of preeclampsia; studies have previously shown a significant improvement in detection by combining with other biophysical, biochemical parameters.

Conclusions: In the present study, PAPPA was not found to be the predictor of preeclampsia.

Keywords: Blood pressure, Pregnancy associated plasma protein A, Preeclampsia

INTRODUCTION

Hypertension is one of the commonest medical complication during pregnancy, and a leading cause of the maternal and perinatal mortality.[1] The incidence of hypertensive disorders in pregnancy varies between 5-10%, and it is rising as the women are postponing their first pregnancy to a older age and increased pre pregnancy weight.[1] On the other hand, the incidence of eclampsia is declining in the industrialised and affluent society due to the better antenatal care and management of pre eclampsia.[1]

Human placentation relies on the trophoblastic invasion of the, maternal decidua, myometrium and their blood vessels. Cytotrophoblastic cells invade and partially replace the endothelium of the maternal spiral artery, leading to progressive dilatation of these vessels. This process begins as Early as the 10th day of post conception and continues throughout the pregnancy.[2,3]

Defective placentation is considered to be the major etiological factor in the development of Pre-eclampsia and intrauterine growth restriction (IUGR), both of which are major causes of Perinatal morbidity and mortality worldwide.[4,5] Uterine artery doppler measurements shows that impedance to the flow in the uterine artery decreases with the gestational age in normal pregnancy. But this impedance to flow is Increased in established preeclampsia and IUGR.[6,7]

Examining of the uterine circulation in the first trimester in order to predict preeclampsia and IUGR, however has been increasingly reported.[8]

Placental products are released during the placentation process. Levels of these products reflect the pathophysiology of defective placentation and its consequences, therefore, there is increasing role in early gestation screening tests for later pregnancy complication. These are Pregnancy associated plasma protein A (PAPPA), placental growth factor (PIGF), soluble FMS-like Tyrosine kinase 1(sFlt-1), soluble endoglin(s Eng), placental protein 13 (PP13), activin A, inhibin A, disintegrin and metalloprotease 12 (ADAM12).[9]

PAPPA is a protease for insulin like growth factor binding protein 4 (ILGFBP 4). A low level of PAPPA is associated with higher ILGFBP 4 and lower free insulin like growth factor (ILGF). Insulin like growth factor 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. Maternal Serum PAPPA has been shown to be relatively low in the first trimester of pregnancies complicated by preeclampsia and/or IUGR.[10] Hence, this study title 'Early trimester prediction of hypertensive disorders in pregnancy using pregnancy associated plasma protein A (PAPPA) 'is designed to focus on the prediction of hypertensive disorders in pregnancy at 11-14 week of gestation.

METHODS

Source of data

Data was collected from the patients admitted in hospitals attached to J. J. M. medical college Davanagere, Bapuji hospital, Davangere, Chigateri General hospital, Davangere and women and child health hospital, Davangere.

Study design, duration, subjects and sample size

Current study is a hospital based prospective screening study conducted for a duration of two years (October 2017 to August 2019) on 200 pregnant women visiting OPD'S for ANC check up. Data analysis was done through IBM SPSS version 22 for windows.

Inclusion criteria

Inclusion criteria for current study were; women with, singleton pregnancy and gestational age of 11-14 week of gestation.

Exclusion criteria

Women with, multiple pregnancy, subjects with past history of preeclampsia, diabetes mellitus, chronic hypertension, renal disease, autoimmune disease, vasospastic or immunological disorders.

Procedure

This prospective study was conducted in three hospitals for a period of 2 years from October 2107 to August 2019, where 200 women with singleton pregnancies between 11-14 weeks of gestation are recruited, which includes 200 antenatal women visiting OPD, fulfilling the inclusion and exclusion criteria. Gestational age was calculated from reliable menstrual history dates and early USG. All women were subjected to detailed history regarding age, parity, past obstetric history, medical history, family history, height, weight, blood pressure were measured. Maternal serum samples were collected via venipuncture. The samples were centrifuged and the serum was stored in deep freezer (-20^0C) and were assayed using PAPPA ELISA kit (DRG PAPPA ELISA EIA-2397, DRG International, Inc .USA). Cut off for PAPPA was taken as, at 11 week <0.8 mIU/ml, 12 week <1.03 mIU/ml, 13 week <1.47 mIU/ml. These women were followed up in ANC clinic and examined every 4 weekly till 28 weeks, then fortnightly upto 34 weeks and thereafter weekly till delivery then upto 12 weeks postpartum. The cases with positive screening test findings are closely monitored and if required early intervention was done to prevent the complications.

RESULTS

Total 23.5% patients are in the age group 21-15 years only, 19% are in the age group of >31 years. 44**%** of the patients are primigravida. Mean age of the women who didn't developed PE is 23.38 years. Mean age of the women who developed GHTN, mild PE, severe PE is 22.67 years, 25.21 years, 24 years respectively. Out of 200 women, 12 % of women had raised SBP and DBP. Prevalence of preeclampsia; 3%, GHTN 7%, mild PE, 2% severe PE. Out of 24 women who developed PIH, 3 women had decreased PAPPA, 21 women had normal PAPPA. And the p<0.455 which is non-significant. Pregnancy associated plasma protein A at 11-14 weeks of gestation has specificity 87%, NPV is 81%. Accuracy of PAPPA is 73% in predicting the PIH at 11-14 weeks. Out of 24 women with PIH, 7 delivered a preterm baby, 17 women delivered at term.
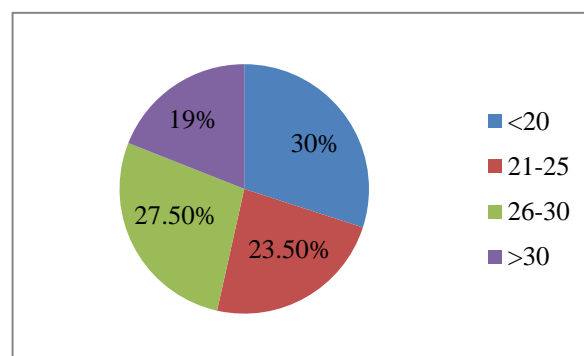

Figure 1: Age distribution of the patients in the study.

Table 1: Parity distribution.

Gravidity	N	%
PRIMI	88	44
Multi	112	56
Total	200	100

Table 2: Mean age distribution of the subjects based on the outcome.

Outcome	N	Mean age	SD
GHTN	6	22.67	3.50
Mild PE	14	25.21	2.83
Severe PE	4	24.00	3.27
Normal	176	23.3	3.79
ANOVA p<0.317 (non significant)			

Table 3: Blood pressure in study group at the time of diagnosis.

Blood pressure		N	%
SBP	<140	176	88
	>140	24	12
DBP	<90	176	88
	>90	24	12

Table 4: Association of the PAPPA with the women who developed PIH.

Outcome	PAPPA		Total
	Decreased	Normal	
PE	3	21	24
Normal	33	143	176
Total	36	164	200
p<0.455 (non significant)			

Figure 2: Prevalence of preeclampsia.

Table 5: Role of PAPPA in prediction of PIH.

Study variable	Sensitivity N (%)	Specificity N (%)	PPV N (%)	NPV N (%)	Accuracy N (%)
PAPPA	9	87	12.50	81	73

Table 6: Analysis of gestational age at the time of delivery.

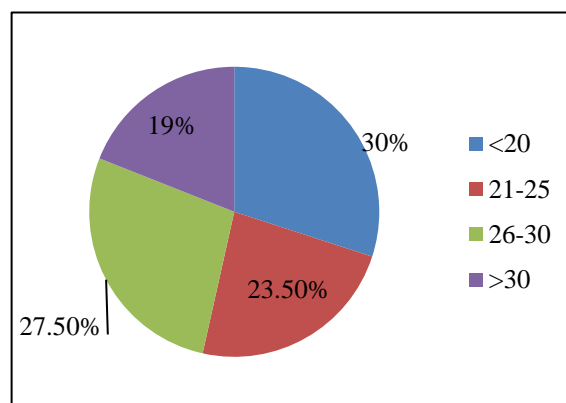| Gestational age	Outcome		Total
	PE	Normal	
Preterm (<37 weeks)	7	26	33
Term (>37 weeks)	17	150	167
Total	24	176	200
Chi square test p<0.07, (non significant)			

DISCUSSION

In our observational study done over a period of two years among 200 women attending the outpatient department for antenatal care at J.J.M. medical college and analysed pregnancy associated plasma protein A (PAAPA) at 11-14 week of gestation. These patients were followed up till delivery and details of pregnancy events, mode of delivery noted. Out of 200 women studied 9% women developed preeclampsia. According to a study, the prevalence of hypertensive disorders in pregnancy was 7.8% with preeclampsia in 5.4% of the study population in India.[12]

Among 200 women 25% women had raised MAP who developed PIH, which can be compared to Poon et al, who described PIH in 2 % of the women with raised MAP at 11-14 week of gestation.[11] A nested case control study done in Netherlands by Kuc et al found first trimester MAP to be one of the most important predictor of preeclampsia.[10] But in the present study, predicting ability of MAP is statistically insignificant (p<0.952) as compared to non PIH patients and hence this will not help in the prediction of PIH which is similar to the study by Narang et al with similar results (p<0.819).[9]

Although a low PAPPA in itself is not a strong indicator of preeclampsia; studies have shown a significant improvement in detection by combining first trimester PAPPA with Uterine artery Doppler velocimetry.[10,13] our study PAPPA alone at 11-14 weeks is not significant in predicting PIH (p<0.455), but when combined with MAP(p value0.000) and UAPI (p< 0.03), we got sensitivity of 77% and 85% respectively. A recent meta-analysis by Velauthar et al, reviewed the accuracy of uterine artery Doppler analysis in first trimester in prediction of IUGR and preeclampsia.[7,2] Eighteen studies involving 55,974 women evaluation, with fifteen of these studies enrolling women with low-risk pregnancies. Uterine artery RI or PI >90th percentile and the presence of notching (unilateral/ bilateral) were used to define the abnormal flow velocity waveforms. An abnormal uterine

artery pulsatatlity index in first trimester was predictive of preeclampsia with sensitivity of 26.4%. In present study, uterine artery pulsatatlity index at 11-14 weeks of pregnancy is found to be the best parameter for prediction of preeclampsia as it had the high sensitivity (29%) and specificity (94%) for identifying the high-risk group. Thus, uterine artery pulsatality index alone is a good screening test for prediction of preeclampsia in first trimester, especially in a developing nation like India where there are limited resources. 89.5% delivered through vagina (16.5% are preterm, 83.5% are term), 10.5% had caesarean delivery.

CONCLUSION

After assessment of inclusion and exclusion criteria 200 antenatal women of 11 to 14 week of singleton pregnancy were selected for the study. After an informed consent woman, PAPPA was measured. These women were followed up clinically for development of preeclampsia. In preeclamptic women 8.3% of decreased PAPPA women developed PIH, with p<0.455 which is not statistically significant.

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