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Original Research Article

An observational study of evaluation of extended first trimester screening test to predict early preterm pre-eclampsia in pregnant women

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ABSTRACT

Background: Pre-eclampsia is hypertensive disorder with several complications. Contributes to increased maternal mortality and morbidity. Pre-eclampsia is associated with pre term labour, IUGR and several other complications like end organ failure in mother. So, it is important to diagnose early and take appropriate steps to mitigate maternal mortality and morbidity. Aim was to detect and predict early preterm pre-eclampsia using extended first trimester screening test in pregnant women. Objectives were to assess the sensitivity and specificity of extended first trimester screening test to predict development pre-eclampsia in pregnancy.
Methods: Method used in this study was observational study.
Results: All three parameters, PAPPA, mean arterial pressure (MAP) and uterine artery pulsatility index found to be significantly associated in predicting early preterm preeclampsia
Conclusions: This screening test enables us to predict preeclampsia before its clinical presentation. It can be used as a reliable and a cost-effective screening test. This will help prevent the progression of the disease by taking necessary timely interventions such as ecosprin administration, close and frequent follow up of screen positive mothers. Thus, it is useful tool in reducing the burden of maternal and fetal morbidity on the health system. This study also has confounding factors due to starting of prophylactic treatment with ecosprin based on ACOG/ NICE guidelines, which increased false positive rate.

Keywords: Pre-eclampsia**,** PAPP-A, MAP, Uterine artery pulsatility index

INTRODUCTION

Pre-eclampsia is a pregnancy-specific hypertensive disorder with serious complications contributing to high maternal and fetal morbidity. About 16% of all pregnancies are complicated by gestational hypertension and pre-eclampsia contributes to be 2-5% all over the world. In India, it is estimated that hypertensive disorders constitute about 7.8% of all pregnancies with pre-eclampsia contributing to 5.4%.[1]

Preeclampsia shows a noteworthy positive association with preterm birth causing a substantial burden to developing countries like India where the availability of and the access to NICU and maternal fetal units are scarce. It gives the impression to be associated with 2-fold increased odds of having NICU admissions on account of SGA babies, respiratory distress, asphyxia or fetal distress.

Although there is an increase in the number of institutional deliveries in India, a staggering 19% of maternal deaths are secondary to pregnancy induced hypertension-WHO 2014. It is therefore essential to detect pre-eclampia as early as possible in pregnant mothers so that, necessary and appropriate interventions can be taken for its prevention and, if prevention is not possible, to ensure safe delivery

of a healthy baby from a healthy mother, by controlling the severity and slowing the progress of pre-eclampsia.

Pre-eclampsia is associated with abnormal biomarkers such as low PAPP-A, elevated fibronectin, PlGF, endoglin much prior to the clinical manifestation of the disease. These biochemical markers can be freely measured in a laboratory, thereby help in screening women for early signs of the disease before its natural progression and help identify women at risk of developing pre-eclampsia and its associated complications.

A large body of data exist that have demonstrated the utility of biochemical markers such as PAPP-A in conjunction with clinical assessment such as MAP and ultrasound measurement of lowest uterine artery pulsatility index (L-PI), in order to predict subsequent development of preterm PE. This is to enable necessary steps and interventions that may be taken in time, to mitigate the ill effects of disease, and if possible, prevent its progression.

In this study we intend to explore the effectiveness of using extended first trimester screening test which is a combination of serum PAPP-A, L-PI and MAP to predict early preterm pre-eclampsia.

METHODS

Study site

The study was conducted at Apollo Hospitals, Chennai based study.

Study population

Pregnant women between the gestational ages of 11 weeks to 13 weeks +6 days enrolled in Apollo Hospital during their routine NT scan.

Study design

The study design was an observational study.

Study duration

The duration of study was from June 2019 to June 2021.

Sample population

Total 206 patients included in the study.

Inclusion criteria

Pregnant women enrolled in Apollo hospital during extended first trimester (11 weeks to 13 weeks +6 days gestation) at the time of NT scan were included in study.

Exclusion criteria

Pregnant women <10 weeks +6 days gestation, pregnant women >14 weeks gestation, molar pregnancy and anomalous foetus were excluded from the study.

Sample size

Since primary goal of the study is to find out the sensitivity and specificity of extended first trimester screening test, we have taken sensitivity of extended first trimester screening test as 84% in detecting PE for working up the sample size using following formula.[17]

$N=(z\times2pq)/d\times2$

Where, N=standard normal variate value=1.96, p=sensitivity of extended first trimester screening triple screening test (84%) q=1-p (16%), d=clinically allowable error (margin of error)=5%. Therefore, required sample size is 206 cases.

Study period

Time frame was of 2 years.

Ethical considerations

Informed consent from the study population was taken prior to commencing the study. Patient information and research data were kept confidential throughout the duration of this study. Patients were educated about pre-eclampsia by way of information leaflets and any doubts they had, were clarified. Research protocol was presented to the institutional ethical board and necessary permissions were taken prior to conduct of study.

Statistical analysis

The data collected are entered in Microsoft excel. The collected data were the analysed with standard statistical packages using IBM SPSS statistics for windows, version 23.0. Armonk, NY: IBM Corp. The maternal characteristics along with MAP, PAPP-A and L-PI was entered as continuous and categorical data. The correlation of maternal MAP, PAPP-A and L-PI with the presence and absence of preeclampsia was assessed. Descriptive statistics, frequency analysis, percentage analysis was used for categorical variables. The mean and Standard deviation were used for continuous variables. To find the significant difference between the bivariate samples in paired groups, the paired t test was used, for independent variables, the unpaired sample t test was used. The receiver operating characteristic (ROC) curve analysis was used to find the sensitivity, specificity with cut off values for correlation of PAPP-A and pre-eclampsia. To find the significance in categorical data Chi square test is used, similarly, if the expected cell frequency is less than 5 in 2×2 tables, Fisher's exact was used. In all the above statistical tools,

the probability value 0.05 is considered significant. The results are depicted in the form of tables and graph. In this study, 206 pregnant women were selected as per the inclusion criteria and were observed for developing pre term preeclampsia. Risk factors are tabulated according to NICE and ACOG guide lines.

RESULTS

MAP of subject group was found to have no statistical significance with pre-eclampsia has a standalone marker (Table 1).

MAP had 66.7% sensitivity and 66.5% specificity in identifying early preterm pre-eclampsia (Table 2).

PAPP-A serum marker of subject group was found to be of high statistical significance with pre-eclampsia has a standalone marker (Table 3).

PAPP-A has 91.7% sensitivity and 87.1% specificity in identifying early preterm pre-eclampsia (Table 4).

Lowest pulsatility index of uterine artery of study group was found to be of no statistical significance with the pre-eclampsia has a standalone marker (Table 5).

L-PI has 75% sensitivity and 76.8% specificity in identifying early preterm pre-eclampsia (Table 6).

Table 1: MAP versus pre-eclampsia.

Variable	Pre-eclampsia	N	Mean	S. D.	T value	P value
MAP	Present	12	1.2	0.2	1.726	0.086 #
MoM	Absent	194	1.0	0.1		

#No statistical significance at p>0.05 level.

Table 2: AUROC of MAP.

Area	P value	95% C. I.		Cut off	1.06
		LB	UB	Sensitivity	66.7%
0.806	0.0005**	0.650	0.962	Specificity	66.5%

**Highly statistical significance at p<0.01 level.

Table 3: PAPP–A versus pre-eclampsia.

Variable	Pre-eclampsia	N	Mean	S. D.	T value	P value
PAPP-A	Present	12	0.4	0.1	16.228	0.0005**
	Absent	194	1.2	0.7		

**Highly statistical significance at p<0.01 level.

Table 4: AUROC for PAPP-A.

Area	P value	95% C. I.		Cut off	0.46
		LB	UB	Sensitivity	91.7%
0.912	0.0005**	0.871	0.954	Specificity	87.1%

**Highly statistical significance at p<0.01 level.

Table 5: L-PI versus preeclampsia.

Variables	Pre-eclampsia	N	Mean	S. D.	T value	P value
L-PI MoM	Present	12	0.86	0.51	1.793	0.075#
	Absent	194	1.06	0.36		

No statistical significance at p>0.05 level.

Table 6: AUROC for L-Pi.

Area	P value	95% C. I.		Cut off	0.84
		LB	UB	Sensitivity	75.0%
0.697	0.022*	0.489	0.904	Specificity	76.8%

*Statistical significance at p<0.05 level.

Table 7: Screen positive versus preeclampsia.

Screening		Pre-eclampsia		Total	χ^2 values	P value
		Absent	Present			
Screen positive	Count	34	12	46	44.321	0.0005**
	%	17.5	100	22.3		
Screen negative	Count	160	0	160		
	%	82.5	0	77.7		
Total	Count	194	12	206		
	%	100	100	100		

**Highly statistical significance at p<0.01 level.

Table 8: AUROC for screen positive.

Area	P value	95% C. I		Cut off	
		LB	UB	Sensitivity	100.0%
0.912	0.0005 **	0.869	0.956	Specificity	82.5%

**High statistical significance at p<0.01 level.

Table 9: Descriptive statistics of study group.

Variables	N	Minimum	Maximum	Mean	S. D.
Age (years)	206	18.0	39.0	28.48	4.21
Weight (kg)	206	44.7	111.1	64.46	10.55
Height (cm)	206	1.47	1.70	1.58	0.06
BMI (kg/m^2)	206	19.00	41.00	25.12	3.67
SBP	206	80.0	140.0	107.48	12.47
DBP	206	50.0	90.0	65.73	10.60
MAP (MOM)	206	0.78	1.39	1.05	0.14
PAPP-A	206	0.23	3.63	1.16	0.67
L-PI (MOM)	206	0.29	2.14	1.10	0.37

Screen positive is considered when one of the three markers are positive. All 12 subjects who developed pre-eclampsia were screen positive for the study. And patient who did not develop preeclampsia were screen negative. Out of 46 screen patient, 12 developed early pre term pre-eclampsia and 34 did not develop any signs of early pre term pre-eclampsia, high false positive screen positive can be due to initiation of treatment in first trimester according to ACOG/ NICE protocol (Table 7).

This study had 100% sensitivity and 82.5% specificity in identifying early pre term pre-eclampsia using first trimester screening tests (Table 8).

Given the test performance in the study and the clinical characteristics associated with preeclampsia and biophysical and biomarkers for preeclampsia a statistical testing is required. To examine the significance of the test results and to test the reliability of biophysical and biomarkers. Tools used were chi square test, independent t test, Fisher's exact test.

DISCUSSION

In this study PAPP-A showed significant ability to detect pre-eclampsia when used along with MAP and lowest uterine artery pulsatile index as a combination screening test. Sensitivity and specificity of independent variables to predict early preterm pre-eclampsia were analysed. Sensitivity and specificity of PAPP-A is 91.7% and 87.1% respectively. Sensitivity and specificity of MAP is 66.7% and 66.5% respectively. Sensitivity and specificity of L-PI is 75% and 76.8% respectively. Screen test results in this study were interpreted as positive even when one of the three markers were positive. Screen positive test for preeclampsia after integrating all the three variables as single combination test, the sensitivity and specificity increased to 100% and 82.5% respectively. In this study, sensitivity of extended first trimester screening test was 100%, and was able to identify all the mothers who developed early preterm preeclampsia accurately. The specificity was 82.5%, and was able to identify normotensive pregnant women with no risk of developing early preterm PE, as truly as 8 out of 10 times. This study shows association of early preterm preeclampsia with maternal characteristics, biophysical and biochemical markers according to all previous studies on pre-eclampsia. All pregnant women participated in the study had chromosomally normal fetus. In her study Poon et al compared the addition of PAPP-A to MAP, L-PI and maternal characteristics and concluded that addition of PAPP-A improves the screening performance along with combination of maternal factors and biophysical in early trimester.[2] My study data shows comparable results to

Poon et al study.[20] In the same study, sensitivity of the test was 84%, but sensitivity in my study is apparently increased because, Apollo being a tertiary care center, high risk patient load is increased, hence the sensitivity of the study has also increased. Mayrink et al in their study, stated that MAP alone cannot determine risk for developing preeclampsia, addition of maternal risk factors will improve the sensitivity.[3] My study has data comparable to this study of Mayrink et al.[3] In my study, the sensitivity of uterine artery pulsatility index is 75%, which is comparable to the study conducted by Khong et al.[4] Due to low sensitivity, uterine artery pulsatility index cannot be used as a single marker for predicting Preeclampsia and needs to be combined with other maternal characteristics and biomarkers. My study also observed, pregnant women with overt diabetes, chronic hypertension, pre-existing renal disease have increased risk for developing pre term preeclampsia, which corresponds with data available in other studies also.

Limitations

Sample size has been reduced to bare minimum requirement, due to COVID-19 pandemic and lesser patient attendance. Some of the study participants were started on treatment for prophylaxis for pre-eclampsia (Administration of ecosprin) based on institutional practice or ACOG/NICE guidelines based on their risk factors. This may have influenced study results as some women on treatment, may not have developed early preterm PE. Study data represents a population cohort that is typical and specific to tertiary care referral hospitals.

CONCLUSION

This study has demonstrated a statistically significant correlation between positive extended first trimester screening test result and development of early preterm preeclampsia. Thus, this screening test enables us to predict pre-eclampsia before its clinical presentation. It can be used as a reliable and a cost-effective screening test. This will help prevent the progression of the disease by taking necessary timely interventions such as ecosprin administration, close and frequent follow up of screen positive mothers. Thus, it is useful tool in reducing burden of maternal and fetal morbidity on health system. This study also has confounding factors due to starting of prophylactic treatment with ecosprin based on ACOG/ NICE guidelines, which increased false positive rate

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