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TO STUDY THE ROLE OF SERUM BIOMARKERS COMBINED WITH UTERINE ARTERY DOPPLER IN PREDICTION OF EARLY ONSET PREECLAMPSIA IN PRIMIGRAVIDAS AT A TERTIARY CARE CENTRE

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ABSTRACT **Background-**The purpose of the study was to evaluate the effectiveness of first and second trimester screening methods in prediction of early onset preeclampsia in primigravida at our centre. Aim and Objective-The objectives was to study the role of first trimester mean arterial pressure, uterine artery pulsatility index and PAPPA-A as well as PLGF in second trimester in prediction of early onset preeclampsia in all primigravidas singleton pregnancy. **Methods-** the study was conducted in the department of Obstetrics and Gynaecology, GSVM medical college Kanpur. A detailed questionnaire were filled, mean arterial pressure (MAP) was recorded, sample were taken for PAPA-A level and UAPI was measured at 11-14 weeks of gestation. Same patients were followed in second trimester at 16-20 weeks of gestation for measurement of MAP, UAPI and serum PLGF level. Follow up was done till 34 weeks of pregnancy for development of early onset preeclampsia. Results- logistic regression analysis was used to assess the predictive power of mean arterial pressure, serum biomarkers and UAPI to predict early onset preeclampsia. In pregnancies that developed early onset preeclampsia the mean arterial pressure and uterine artery PI was increased whereas levels of PAPP-A and PLGF were decreased. **Conclusion-** study demonstrate that no single biomarker alone is effective for prediction of early onset preeclampsia and combination of these serum biomarkers, mean arterial pressure and UAPI in both first and second trimester has the highest predictive value in prediction of early onset preeclampsia but not of much significance in detection of late onset preeclampsia.

KEYWORDS : Pregnancy Associated Plasma Protein-A (PAPP-A), Preeclampsia, Uterine Artery Pulsatility Index (UAPI), Placental Growth Factor (PLGF).

INTRODUCTION

Preeclampsia complicates about 3% of all pregnancies and all hypertensive disorders affect about 5% to 10% of pregnancies worldwide.[1] The screening test to predict preeclampsia would be a powerful tool in preventing early onset preeclampsia-induced maternal morbidity and mortality especially in developing nations where high-risk specialists are limited.[2-3] Pathogenesis of preeclampsia still requires elucidation. It's a complex interaction between immunological factors and genetic factors.[4] Placental ischemia, oxidative stress resulting in inadequate trophoblastic invasion leads to increased resistance in uterine artery blood flow.[5] The early diagnosis of PE still remains a challenge. Effective screening for pre-term pre-eclampsia can be provided at 11-13 weeks gestation by assessment of a combination of maternal characteristics with multiple of the median (mom) values of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI) and serum placental growth factor (PLGF) and pregnancy associated plasma protein-A (PAPP-A).In pregnancies with PE the deviation from normal for each biomarker was inversely related to the gestational age at delivery and consequently , the performance of screening was better for early than late PE. A number of biomolecules which could be potential marker of early onset PET has been extremely helpful mainly include PLGF and PAPP-A have been gathered great attention. These serum biomarkers (PLGF and PAPP-A) is promising initiative tool for screening of PET if combined with mean arterial pressure and uterine artery Doppler. In May 2019, FIGO released guidelines to combat preeclampsia and calls for all women to receive first-trimester screening. First trimester screening would represent a major advantage over a second trimester approach since it open prospects for early and more effective intervention.

MATERIALS AND METHODS

This was a prospective observational study conducted from January 2019 to July 2020 in department of obstetrics and Gynaecology, GSVM medical college Kanpur, Uttar Pradesh. Inclusion Criteria; All primigravidas in their first trimester of pregnancy and had of age >18 years with singleton pregnancy who were willing to participate in the study. Exclusion Criteria; Patient who did not give consent had age >40 years & <18 years, molar pregnancy, multifetal pregnancy, Obesity [BMI>35KG/M2], history of smoking, patients of chronic hypertension, chronic kidney disease, patients with gross fetal chromosomal anomalies. Ethical clearance was obtained from ethics committee GSVM medical college, Kanpur with reference no. EC/BMHR/2019/30 Dated 22-05-2019.

The sample size has been calculated from formula:
$N \geq Z21\text{-}\alpha/2\ p(1\text{-}p)/d2$

When z $1\text{-}\alpha/2$ is the Z value for $\alpha = 0.05$ (1.96)p is the expected proportion we have used the detection rate of P.E by MAP and history combined as reported by Leone C.Y POON et al 2008.
$N \geq 37$ for allowable $\approx$ error of 5% of p.
Therefore a sample size of 40 has been calculated.

METHODOLOGY

After taking informed and written consent enrollment was done. A detailed questionnaire was filled which included particulars like socioeconomic status, demographic factors, obstetric history and body mass index. After routine antenatal examination mean arterial pressure was recorded. The blood pressure was measured in both the arms simultaneously in seated position with arms supported at the level of the heart by 2 digital sphygmomanometers (Model –HEM-7121, Omron healthcare co. Ltd. Japan) using a normal (22 to 32 cm) adult cuff. After rest for 5 minutes, BP again measured and a series of recordings was made at one minute interval until variations between consecutive readings fell within 10 mm Hg in systolic and 6 mm Hg in diastolic BP in both arms. Then the MAP of each arm (using the average of the last 2 stable measurements) was calculated by the formula: MAP = DBP + 1/3 (SBP - DBP) where DBP – diastolic BP, SBP - systolic BP. The arm with the highest final MAP was taken for the subsequent analysis of results. Uterine artery Doppler was done in our department performed by the same experienced sonographer according to the ISUOG Practice Guidelines (2013) for use of Doppler Ultrasonography in Obstetrics. After emptying the bladder the woman was laid in supine position. Transabdominally, the crown rump length or biparietal diameter was obtained and placental localization was done. A midsagittal section of the uterus according to gestational age was obtained and the cervical canal identified. The probe then moved laterally until the paracervical vascular plexus was seen. Colour doppler was turned on and the uterine artery was identified as it turned cranially to make its ascent in to the uterine body. Measurments of UtA-PI was taken at this point before the uterine artery branched into the arcuate arteries and the same process was repeated on the

contralateral side. The pulsatility index (PI) was measured bilaterally and the mean PI of the both uterine arteries were calculated. The presence of early diastolic notch was also recorded. Maternal serum samples for testing was collected via venepuncture. The samples were centrifuged @ 4000 rpm for 15 mints and the serum was stored in a deep freezer (- 20 ºc) and were assayed using PAPP-A and PLGF ELISA- k kit. Women who were enrolled in our study were kept on follow up. Patients were called for antenatal visits every 2 weeks till 36 weeks and weekly thereafter. The target condition was PE, as defined by International Society for the Study of Hypertension in Pregnancy as systolic blood pressure > 140 mmHg and/or diastolic blood pressure of ≥90 mmHg on at least 4 hrs apart developing after 20 weeks of gestation in previously normotensive women were considered. If hypertension developed before 34 wks, it was classified as early onset PE and if it develop after 34 wks the pregnancy was diagnosed as the late-onset PE. The study continued till the optimum sample size was achieved with in the given duration. The data was recorded in multiples of median and statistically analyzed using Microsoft excel version 2010 and statistical software SPSS version 17, conclusions were drawn accordingly. The sensitivity and specificity for different cut-off of each variables in detecting preeclampsia were calculated and depicted as receiver operating characteristic (ROC) curves. Multiple logistic regression analysis was used to assess the predictive power of mean arterial pressure(MAP), PAPP-A, PLGF, UTERINE ARTERY PI. The prespecified analysis for performance of screening by maternal factors and any combination of maternal factors with MAP, UtA-PI, PAPP-A and PLGF were estimation of areas under the receiver operator characteristic curve (AUC). Results were evaluated at 95% confidence interval and significance was evaluated at $p<0.05$ level.

RESULTS

During the study period, 40 pregnancies met the inclusion criteria and underwent screening for PE, out of which 10 patients develop early onset preeclampsia, 2 patients landed in late onset preeclampsia, 5 patients develop HELLP syndrome and 1 patient landed in eclampsia. There were 22 gestational age matched normal pregnancies as control.[Table 1]

TABLE 1: DIFFERENT OUTCOMES OF THE AFFECTED WOMENS

	Number	Percentage (%) of the total (n=40)
Early onset PE	10	25%
Late onset PE	2	5%
HELLP syndrome	5	12.5%
Eclampsia	1	2.5%
Total	40	45%

At the time of blood sampling there was no statistically significant difference in maternal age, body mass index and gestational age between the women that developed preeclampsia and the controls. Study population who developed EARLY ONSET PE largely comprised of age group more than 30 years (elderly).Logistic regression analysis was used to assess the predictive power of MAP, PAPP-A LEVEL and UAPI to predict EARLY ONSET PRE –ECLAMPSIA in first and Second trimester.

TABLE 2: ASSOCIATION OF MAP, PAPP-A LEVEL AND UAPI WITH THE DEVELOPMENT OF EARLY ONSET PET SYNDROME IN FIRST TRIMESTER (11-14 WEEKS)

EARLY ONSET	B	S.E.	Sig.('p')	O.R.	95% C.I .for O.R.	
					Lower	Upper
MAP	2.76	1.404	0.049	15.892	1.014	249.090
UAP 1 PAPP-A level	3.83 -4.75	1.424 1.28	0.007 0.000	46.305 111.1	2.839 9.25	755.217 999

Table 2 shows there were higher chances of patient landing in to EARLY ONSET PE if MAP was higher, level of PAPP-A was low and value UAPI was raised in first trimester. The regression co-efficient for MAP was statistically significant with p-value=(0.049) and ODD RATIO=15.892(95./. CI) 1.014 to 249.090. The regression co-efficient for PAPP-A is statistically significant with p- value=(0.000) and ODD RATIO =111.1(95./.CI) 9.25 to 999. This implies that if low value of PAPP-A is found in first trimester then the chances of patient landing in to EARLY ONSET PET are atleast 9.25 times more than otherwise. Raised value of UAPI is statistically also significant, p=0.007 and ODD RATIO=46.305(95./.CI) 2.839to755.217 this implies that if value of UAPI increases in first trimester than the chances of patients landing in to EARLY ONSET PET is 2.8 times is more than otherwise.

TABLE 3: ASSOCIATION OF MAP, PAPP-A LEVEL AND UAPI WITH THE DEVELOPMENT OF EARLY ONSET PET IN SECOND TRIMESTER (16-20 WEEKS)

EARLY ONSET PE	B	S.E.	Sig.	Exp(B)	95% C.I. for EXP(B)	
				Lower	Upper	
MAP	.981	.791	.215	2.667	.566	12.557
PLGF level	-3.584	.998	.000	.028	5.10	250
UAPI 2	60.536	23679.797	.998	1.95e+26	.000	.

Table 3 shows the regression co-efficient for PLGF LEVEL is statistically significant, p-value= (0.000) and ODD RATIO=0.028(95./. CI) 5.10 to 250. The regression co-efficient for MAP and UAPI are statistically not significant, p=0.215 and 0.998 respectively therefore on the basis of available data we cannot conclusively says that raised MAP and raise value of UAPI predict EARLY ONSET PET.

DISCUSSION

In developing countries with limited access to health care facilities pre-eclampsia is a cause for about one third of maternal mortality and therefore early detection of PE is imperative and non-invasive diagnostic methods based on biomarkers hold the promise(8). The performance of each biomarker in combination with maternal factors was superior to that of screening by maternal factors alone. Similarly the performance of screening by a combination of two or more biomarkers was superior to that by individual biomarkers. In recent years, new screening protocols have been introduced in literature by FETAL MEDICINE FOUNDATION with the combined evaluation of maternal characteristic & UtA Doppler examination which was strongly associated with placental and endothelial dysfunction. Our study evaluated mean arterial pressure, PAPP-A level and uterine artery pulsatility index in first trimester showed a statistically significant association between these parameters and early onset PE.[Table2] Thilaganathan B et al [6] in their study shows maternal serum markers and uterine artery mean resistance index are independent predictors of pre-eclampsia. Wright D et al [7] shows in pregnancies with PE there was an inverse correlation between multiple of the median values of the uterine artery PI and MAP with gestational age at delivery. Screening by maternal characteristics, uterine artery PI and MAP detected 90% of PE cases requiring delivery before 34 weeks and 57% of all PE cases at a fixed false-positive rate of 10%. Study revealed a new model can be developed based on these parameters for effective first-trimester screening for PE. Study found that there was significant reduction in level of PAPP-A in case of early onset pre-eclampsia while the level of PAPP-A in the late onset pre-eclampsia did not differ from the control group concluding that first trimester PAPP-A is useful in predicting early onset pre-eclampsia. Petla LT et al [8] study suggested that larger trials are required to confirm these preliminary predictions. Gallo D et al [9] Study screened primigravida patients by measurement of MAP in first trimester as well as MAP in second trimester, the detection rate at FPR of 10%, were 84.3, 65.7 and 52.5 %.Study concluded that performance of screening for PE by MAP is best when measurements are taken at both 11-13 and 20-24 weeks gestation than at only one of these gestational ranges. Gujral k et al [10] Study found that no single test is supported by robust evidence to predict early onset PE and screening based on risk factors has low sensitivity. It's better to use combination of uterine artery Doppler, maternal serum biomarkers, and maternal characteristics to offers best predictive power at the moment. Sharma N et al [11] studied that presence of high pulsatility was a significant risk factor for early onset PE and conclude that uterine artery Doppler can be safely performed at the time of routine target anomaly scan in second trimester. Choorakuttil RM et al [12] studied that in screening of preterm PE by a combination of maternal factors, MAP, UAPI and PLGF the detection rate was 82% which was higher than that of the NICE method by 41.6% (95% CI,33.2-49.9). Shinde T et al [13] conducted a prospective study on 240 antenatal women and concluded that uterine artery mean PI at 11-14 weeks of gestation is a cost effective predictive test for hypertensive disorders of pregnancy and the recommended reference valve for Indian population is of 2.28.Logistic regression analysis of our study shows a statistically significant correlation between PLGF level and early onset PE in second trimester with p-value of (0.000) and odd's ratio of 0.028(95./. CI) 5.10 to 250 although there was no

significant association found between mean arterial pressure and uterine artery pulsatility index measured in second trimester with development of early onset pre-eclampsia.[Table3] While its seems that prediction of preeclampsia is technically feasible using PAPP-A level, UtA-PI and PLGF level, the cost benefit balance of this screening needs to be further evaluated.

Limitations 0f Study

The study has little limitation-a small sample size, higher rate of illiteracy leading to poor compliance to questionnaire and follow up.

CONCLUSION

We concluded that no single biomarker has alone has the potential to predict early onset preeclampsia. Its role in prediction of preeclampsia. The combination of these serum biomarkers with mean arterial pressure and uterine artery doppler has the highest predictive value in screening of early onset preeclampsia but has only limited importance in detection of late onset preeclampsia. Larger studies are needed to justify the introduction of these biomarkers into routine clinical practice as a prediction of model for preterm preeclampsia. In the future new techniques will hopefully provide sets of multiple markers which will lead to an innovative screening programme clinically more relevant so that early prophylactic strategies could be made for high risk women. We are still in hope that our study will contribute towards the ultimate goal of identifying the best prediction marker(s) and improve the management of women destined to develop preeclampsia.

Author's Contribution:

AS- concept and study design, prepare first draft of manuscript, review of data, interpretation of results, revision of manuscript. KP- review of manuscript, interpretation of results.PL-preparation of manuscript, data collection and analysis, preparation of tables and figures.

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Abbreviations:

MAP : Mean Arterial Pressure , PAPP-A : Pregnancy Associated Plasma Protein-A , UtA-PI : Uterine Artery Pulsatility Index , PLGF : Placental Growth Factor , PE : Preeclampsia , PET : Preeclampsia Toxemia , C.I : Confidence Interval , S.E : Standard Error , Sig. : Significance, O.R : Odd Ratio , B : Unstandardized coefficients(used in regression equation)

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