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Original Research Article

Screening Tests for Early Prediction of Pre-eclampsia

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Abstract:

Background: Preeclampsia (PE) is a multisystem hypertensive disorder of pregnancy characterized by hypertension and proteinuria after 20 weeks of gestation and remains a leading cause of maternal and perinatal morbidity and mortality worldwide. In India, its prevalence ranges from 8–10%, contributing significantly to adverse maternal and neonatal outcomes. As clinical manifestations appear late, the major challenge in obstetrics is the early identification of asymptomatic women at risk. Evidence suggests that biochemical and biophysical alterations occur early in pregnancy, making first-trimester screening a potential strategy for early prediction and prevention of severe disease.

Aim: To evaluate the efficacy of selected biochemical and biophysical markers in the early weeks of gestation as screening tools for early prediction of preeclampsia.

Methodology: This hospital-based prospective observational study was conducted at Tertiary care center, over a period of one year, from October 2020 to September 2021. One hundred normotensive, non-proteinuric pregnant women between 11–13 weeks of gestation were initially recruited. After exclusions and loss to follow-up, 52 women were included in the final analysis. Maternal demographic parameters, mean arterial pressure (MAP), serum inhibin A, urinary microalbuminuria, urine albumin-to-creatinine ratio (UACR), and uterine artery pulsatility index (UAPI) at first and second trimesters were assessed. Participants were followed until delivery to document the development, onset, and severity of preeclampsia, mode of delivery, gestational age at delivery, and neonatal outcomes. Statistical analysis included Student's t-test, Chi-square test, Pearson's correlation, and ROC curve analysis using SPSS version 24.0.

Results: Preeclampsia developed in 13.5% of women. Compared to normotensive pregnancies, women who developed PE had significantly higher BMI, MAP, inhibin A, microalbuminuria, UACR, and UAPI in both trimesters ($p < 0.05$). These women also had significantly lower gestational age at delivery, reduced birth weight, and poorer APGAR scores. UACR and microalbuminuria demonstrated high sensitivity, while inhibin A and UAPI showed high specificity for PE prediction. Caesarean delivery rates were higher in the PE group.

Conclusion: A combination of biochemical markers (inhibin A, microalbuminuria, UACR) with biophysical markers (MAP and uterine artery Doppler) in early pregnancy provides an effective screening approach for early prediction of preeclampsia. Early identification of high-risk women allows timely surveillance and preventive interventions, potentially improving maternal and perinatal outcomes.

Keywords: Preeclampsia, Early prediction, Inhibin A, Uterine artery Doppler, Microalbuminuria.

Introduction

Preeclampsia (PE) is a multi-system disorder manifested primarily by hypertension and proteinuria during the second half of pregnancy. It is the most common of all pregnancy-related medical complications and affects approximately 5 to 7% of pregnancies worldwide. In India, the prevalence of PE ranges from 8-10%, contributing to maternal (12 to 15%) and perinatal (24%) mortality. The incidence is more in nulliparity around 15%, and in multiparas around 10%. [1,2] The global incidence of pregnancy-induced hypertension is reported to be 3-18%. [3] If untreated, pregnancy hypertension can progress to PE and eclampsia, which are life-threatening. [4]

PE is a hypertensive disorder with proteinuria, which can lead to edema, impaired perfusion of the uteroplacental unit, and subsequently to fetal growth restriction. PE contributes substantially to increase the morbidity and mortality of both mother and newborn. [5] PE subdivided into early-onset PE (occurs before 34 weeks of gestation) and late-onset PE (occurs after 34 weeks of gestation), the former is associated with a higher incidence of adverse outcome. [6-9]

The major challenge in modern obstetrics is early identification of pregnancies at high risk of developing PE and undertaking the necessary measures to reduce the prevalence and severity of the disease. [10] The definitive etiology being unknown, its prevention becomes a difficult task. Even though PE usually occurs from the late second to the third trimester, evidence of organ pathophysiology found at very early stages of pregnancy.

Therefore we need a widely applicable and affordable test that could permit presymptomatic diagnosis to identify and monitor the women for better antenatal surveillances. The study aims to evaluate the screening efficacy of different maternal serum, urinary biomarkers, and Doppler ultrasonography during the early weeks of gestation for early detection of PE and to take the necessary measures to prevent the progression of the condition to a severe form.

Aim: To evaluate the efficacy of different biochemical and biophysical markers in the early weeks of gestation as screening tools for early prediction of preeclampsia.

Objective: Screening of asymptomatic pregnant women to categorize into high risk and low risk and To provide better antenatal surveillance for high -risk women to reduce both maternal and perinatal morbidity and mortality. To prevent the early-onset or severe PE and its associated complications.

Materials & Methods

This study is a hospital-based prospective observational study done in 100 pregnant women in the Department Obstetrics and Gynaecology department, conducted at Tertiary care center, over a period of one year, from October 2020 to September 2021.

This study is to analyze the maternal demographic characteristics, serum markers, urinary markers, and ultrasound doppler among normotensive, non -proteinuric women who were attending the outpatient as well as those admitted in antenatal ward in the first trimester(11-13 weeks).

Out of 100, 5 members were terminated due to lethal congenital anomalies, 6 women had miscarriages, 9 members were changed their place, 4 women developed gestational diabetes, 10 members withdrew their consent in subsequent visits, 2 pregnancies complicated by Ante Partum Haemorrhage (APH), 4 members landed in a preterm delivery and 8 members were lost follow-up and hence were excluded

from the study.. Only 52 women included in the final analysis.

Inclusion Criteria: Primigravidae and second gravidae less than 13 weeks of gestation will be recruited with normal BP and renal function and no evident proteinuria upon measurement with a dipstick.

Exclusion Criteria: Pregnant women with H/O smoking and alcoholism, Pregnant women with gestational diabetes, overt diabetes mellitu s, previous h/o PIH, cardiovascular disease, anemia, and multiple pregnancies, Pregnant women with chronic liver and kidney disease, chronic hypertension (HTN), chronic urinary tract infection, and other chronic diseases that interfere with the study. Any maternal or fetal condition that requires termination of pregnancy (congenital malformations like Downs syndrome). Active vaginal bleeding.

Methodology: After informed written consent, blood samples were collected from the antecubital vein and allowed to clot in plastic tubes at room temperature. These samples transported to the laboratory within 30minutes of collection. After centrifugation at 1000rpm for 15min, serum from the samples was separated and stored at -20°C until assayed for inhibin A. The serum Inhibin A estimation is done by the chemiluminescent immunometric assay (CLIA) method. All the values expressed in pg/ml.

Between 11 and 13 weeks of gestation, all women who enrolled in a study given a sterile urine container without preservative, and after instruction, a random midstream clean catch urinary sample collected. Routine microscopy was done to exclude urinary tract infection (UTI), and samples analyzed for microalbuminuria and spot albumin-to- creatinine ratio. Urine albumin measured by the immunoturbidimetric method using a commercially available kit (Beckman Coulter) through AU 480 fully automated biochemistry analyzer. Urine creatinine measured by a modified kinetic Jaffe reaction without deproteinization. Urine Albumin (mg/L) =UACR in µg/mg or mg/g Urine creatinine (mg/dl) Interconversion of units: UACR (1 mg/g=1 µg/mg= 0.113 mg/mmol). Dividing the UACR by 8.84 converts the units (from µg/mg or mg/g to mg/mmol).

Uterine artery Doppler: Uterine artery Doppler velocimetry was done at 11-13 weeks and 19-22 weeks of gestation by PHILIPS HD11XE transabdominal ultrasound machine using a 4-6 MHz probe through transabdominal method. Imaging of flow velocity waveforms of the right and left uterine arteries with the patient in a semi-recumbent position, and the uterine artery identified. The recording made at the point where the uterine artery and the external iliac artery appeared to have crossed each other, it is detected by color Doppler. Pulsed wave Doppler was used for obtaining three consecutive waveforms, and the pulsatility index (PI) was measured. The same process repeated on the opposite side, and the mean PI of the two vessels calculated. Blood pressure was measured at each visit, and mean arterial pressure calculated at mid-trimester. All the pregnant women followed till delivery, and blood pressure measured at the third trimester and proteinuria estimation was done and identified the women who developed preeclampsia and note the onset, severity, mode of delivery, and birth weight at the of delivery and compared in both groups.

Statistical Methods: The results will be subjected to appropriate statistical analysis. The data will be tabulated and analyzed. Statistical analysis was done by applying Students unpaired T-test, Pearson's correlation coefficient, Chi-square test, ROC curve. Statistical software: The data obtained were analyzed using IBM SPSS software version 24.0 to generate graphs and tables.

Results

Table 1: Preeclampsia- primigravidae versus (vs.) multigravidae

PE					
No				Yes	Total
Parity	Primi	No. of women	25	5	30
		% within Parity	83.3%	16.7%	100.0%
		% within PE	55.6%	71.4%	57.7%
	Multi	No. of women	20	2	22
		% within Parity	90.9%	9.1%	100.0%
		% within PE	44.4%	28.6%	42.3%
Total		No. of women	45	7	52
		% within Parity	86.5%	13.5%	100.0%
		% within PE	100.0%	100.0%	100.0%
Chi square value=0.625 p value- 0.429					

Table 2: Variables Normotensive vs. Preeclampsia

Variable	Normotensive(n=45) (mean+/- sd)	Preeclampsia(n=7) (mean+/- sd)	t-value	p-value
Mean age(yrs)	24.18+/-4.628	23.14+/- 3.436	0.566	0.574 NS
Mean BMI (kg/m2)	25.26+/-2.82	30.9+/-3.15	-4.838	<0.0001VHS
Mean MAP (mm of Hg)	87.23+/-4.97	105.13+/-5.84	-8.662	<0.0001VHS
Inhibin A(MoM)	1.03+/-0.488	2.10+/-0.77	-4.979	<0.0001VHS
Microalbuminuria (mg/L)	10.99+/-7.007	40.48+/-31.81	-2.444	0.049SIG
UACR (mg/g)	12.84+/-5.61	27.67+/-11.60	-5.504	<0.0001(VHS)
UAPI at 1st trimester (MoM)	0.96+/-0.19	1.34+/- 0.20	- 4.777	<0.0001(VHS)
Mean UAPI (MoM)	0.95+/-0.24	1.45+/-0.17	-5.210	<0.0001(VHS)
Mean GA at delivery (wks)	39.02+/-0.81	36.35+/-1.78	3.901	0.007 SIG
Mean B.WT (kg)	3.016+/-0.26	2.19+/- 0.59	3.580	0.010 (SIG)

Table 3: Mode of delivery (MOD) - normotensive vs. preeclampsia

PE					Total
No				Yes	
MOD	NVD	No. of deliveries	26	2	28
		% within MOD	92.9%	7.1%	100.0%
		% within PE	57.8%	28.6%	53.8%
	LSCS	No. of deliveries	19	5	24
		% within MOD	79.2%	20.8%	100.0%
		% within PE	42.2%	71.4%	46.2%
Total		No. of deliveries	45	7	52
		% within MOD	86.5%	13.5%	100.0%
		% within PIH	100.0%	100.0%	100.0%
Chi-square value = 2.079, P-Value = 0.149 (Not Sig.)					

Table 4: Mean APGAR 1st and 5th minute- normotensive vs. preeclampsia

Variable	Normotensive(n=45) (mean+/- SD)	Preeclampsia(n=7) (mean+/- SD)	t- value	p-value
APGAR 1st min	6.60+/-1.03	4.71+/-1.38	4.301	<0.0001 VHS
APGAR 5th min	8.42+/-0.91	6.71+/-1.38	3.617	0.016 SIG

Table 5: Comparison of onset of PE - primigravidae vs. multigravidae

			Onset			Total
			No	Early	Late	
Parity	Primi	No. of women	25	3	2	30
		% within Parity	83.3%	10.0%	6.7%	100.0%
		% within Onset	55.6%	75.0%	66.7%	57.7%
	Multi	No. of women	20	1	1	22
		% within Parity	90.9%	4.5%	4.5%	100.0%
		% within Onset	44.4%	25.0%	33.3%	42.3%
Total		No. of women	45	4	3	52
		% within Parity	86.5%	7.7%	5.8%	100.0%
		% within Onset	100.0%	100.0%	100.0%	100.0%
Chi-square value = 0.674, P-Value = 0.714 (Not Sig.)						

Table 6: Comparison of the severity of PE- primigravidae vs. multigravidae

			PE			Total
			No	Mild	Severe	
Parity	Primi	No. of women	25	3	2	30
		% within Parity	83.3%	10.0%	6.7%	100.0%
		% within PE	55.6%	75.0%	66.7%	57.7%
	Multi	No. of women	20	1	1	22
		% within Parity	90.9%	4.5%	4.5%	100.0%
		% within PE	44.4%	25.0%	33.3%	42.3%
Total		No. of women	45	4	3	52
		% within Parity	86.5%	7.7%	5.8%	100.0%
		% within PE	100.0%	100.0%	100.0%	100.0%
Chi-square value = 0.674, P Value = 0.7147 (Not Sig.)						

Table 7: Variables at mid-trimester - primigravidae vs multigravidae

Variable	Primigravidae (mean+/-SD)	Multigravidae (mean+/- SD)	T value	P Value
Mean MAP (mm of Hg)	90.78+/-8.77	88.07+/-6.58	1.218	0.229 NS
Mean inhibin A (MoM)	1.30+/-0.69	1.00+/-0.52	1.681	0.099 NS
Microalbuminuria(mg/L)	14.16+/-8.11	16.05+/-23.45	-0.363	0.719 NS
UACR (mg/g)	15.60+/-6.14	13.80+/-10.67	0.766	0.447 NS
Mean UAPI 1st trimester (MoM)	0.98+/-0.22	1.04+/-0.30	-0.839	0.405 NS
Mean UAPI 2nd trimester (MoM)	1.01+/-0.30	1.02+/-0.28	-0.059	0.953 NS

Table 8: Statistics of markers

Variables	UACR	Albuminuria	Inhibin_A	UAPI@1st TRI	UAPI@2nd TRI
Cut-off value	>21.5	>15.2	>1.47	>1.13	>1.20
Sensitivity (%)	85.71	100.00	71.43	71.43	100.00
Specificity (%)	91.11	71.11	95.56	95.56	84.44
PPV (%)	60.00	35.00	62.5	71.43	50.00
NPV (%)	97.62	100.00	95.45	95.56	100.00

Discussion

Preeclampsia is a multisystem disorder of unknown etiology with hypertension, proteinuria, and edema, predisposing to potentially lethal complications such as eclampsia, abruption placentae, circulatory collapse, cerebral hemorrhage, and hepatorenal dysfunction.

The pathophysiology of preeclampsia is not known. There is proof that increased proliferation of the underlying cytotrophoblast in preeclampsia. It may be due to the repair of the ischemic damage to the surface syncytiotrophoblast. These changing processes of damage and repair may cause the functional alteration of the surface layer of syncytiotrophoblast in the PE placenta, and this may explain the increase in the concentration of the biophysical and biochemical markers. In the present study, we evaluate the screening efficacy of maternal demographic characteristics, biophysical (MAP, uterine artery Doppler), and biochemical markers (inhibin A, microalbuminuria, UACR) in the first trimester for early prediction of PE and categorize into high-risk women.

Table 9: Mean maternal age- preeclampsia vs. Normotensive and Incidence of PE

Study	Maternal age (yrs)			Incidence
	Preeclampsia (mean+/-sd)	Normotensive (mean+/-sd)	P value	
M.N EL-Gharib & M. Morad [11]	28.50+8.17	28.60+6.65	0.952 NS	
Narang S et al [12]	26.48	25.61	0.33 NS	11.54%
K Fatema et al [13]	26+/-5	25+/-4	0.49 NS	8.4%
Zadeh et al [14]	25.9+/-4.9	26.5+/-5	0.712 NS	
N.YU. et al [15]	30.2+/-4.6	28.6+/-2.3	0.452 NS	
Present study	23.14+/-3.43	24.18+/-4.62	0.574 NS	13.4%

Table 10: Incidence of PE - primigravidae vs. multigravidae

Study	Normotensive		Preeclampsia		
	Primi	Multi	Primi	Multi	P value
Poon et al [16]	46.3%	51.4%	62.7%	17.6%	<0.05 SIG
Akolekar et al [17]	47.8%	49.3%	58%	24%	<0.016 SIG
Sharma et al [18]	44.3%	55.63%	42.2%	57.8%	0.22 NS
Present Study	55.6%	44.6%	71.4%	28.6%	0.429 NS

Table 11: Mean BMI - preeclampsia vs. normotensive

Study	Mean	Bmi(kg/m2)	
	Preeclampsia	Normotensive	P value
Salomon et al [19]	23.21	22.03	>0.05 NS
K fatema et al [13]	24.54	22.68	0.11 NS
Narang S et al [12]	24.36	24.59	0.803 NS
Poon et al [16]	27.0	24.7	0.004 SIG
Zhang et al [20]	23.28	20.90	<0.05 SIG
N.Y.U. Et al [15]	33.6+/-9.2	28.2+/-6.9	0.033 SIG
Present study	30.90	25.26	<0.001 VHS

Table 12: Mean mid-trimester MAP - preeclampsia vs. normotensive

Study	Mean	Map	
	Preeclampsia	Normotensive	P value
Gallo et al [21]	1.06 MoM	0.99 MoM	<0.001 VHS
Jadli et al [22]	120 mm of Hg	83.3 mm of Hg	<0.0001 VHS
Present study	105 mm of Hg	87.2 mm of Hg	<0.0001 VHS

Table 13: Mean inhibin A- preeclampsia vs. normotensive

Study	Cutoff	Mean	Inhibin a	
		Preeclampsia	Normotensive	P value
MN El Gharib & M Morad [11]	>295 pg/ml	570.00+/-204.55 (pg/ml)	174.52+/-58.99 (pg/ml)	0.0001 VHS Sensitivity 85.7% Specificity 98.5%
Muttukrishn et al. [23]	272 pg/ml	3 ng/ml	0.36 ng/ml	<0.05 SIG
K. Spencer et al [24]	2.00 MoM	286.64 pg/ml	231.13 pg/ml	-
N. Jsebire et al [25]	1.4 MoM	233 pg/ml	167 pg/ml	<0.05 SIG
Cuckle et al [26]	2.01 MoM	> 2.01 MoM	<2.01 MoM	<0.001 VHS
Present study	1.47 MoM	2.10 MoM	1.03 MoM	<0.0001 VHS Sensitivity 71% Specificity 95%

Table 14: Mean microalbuminuria: preeclampsia vs. normotensive

Study	Cutoff	Microalbuminuria		
		Preeclampsia	Normotensive	P value
Inder pal kaur et al [27]	14.8 mg/l	66.59+/-48.76	19.4+/-5.71	<0.05 SIG
Shaarawy et al [28]	20 mg/l	>20 µg/ml	<20 µg/ml	SIG
Present study	15.2 mg/l	40.48+/-31.81	10.99+/-7.00	0.049 SIG Sensitivity 100% Specificity 71%

Table 15: Mean UACR: preeclampsia vs. normotensive women

Study	ACR		
	Preeclampsia	Normotensive	P value
Poon et al [16]	0.87 mg/mmol	0.53 mg/mmol	<0.001 SIG
Upadhyay A et al [29]	>0.2	<0.2	<0.001 SIG Sensitivity 75% Specificity 89.6%
Devi lt et al [30]	>12.27 mg/g	<12.27 mg/g	<0.05 SIG
Gupta et al [31]	30.79 mg/g median	5.2 mg/g median	0.0001 VHS Sensitivity 67% Specificity 76%
Present study	27.67+/-11.60 mg/g	12.84+/-5.61 mg/g	<0.0001 VHS Sensitivity 85% Specificity 91%

Table 16: Mean uterine artery PI at first trimester- preeclampsia vs. normotensive

Study	Cut off	UAPI (mean)			
		Weeks	Preeclampsia	Normotensive	P Value
Narang s et al [12]	>1.70	11-14	1.94+/-0.55	1.42+/-0.44	<0.001 SIG Sensitivity 75.9% Specificity 79.2%
Akolekar et al [17]		11-13	1.02 MoM	1.47 MoM	<0.0001 VHS
Casmod et al [32]		11-14	>1.5	<1.5	<0.05 SIG
Spencer et al [24]		11-14	1.56 MoM	1.02 MoM	0.0001 VHS
Presen study	>1.13	11-13	1.34+/-0.20 MoM	0.96+/-0.19 MoM	<0.0001 VHS Sensitivity 71.4% Specificity 95.5%

Table 17: Mean second-trimester UAPI- preeclampsia vs. normotensive women

Study		Mean uterine	ARTERY PI	
	Weeks	Preeclampsia	Normotensive	P value
Elisa llubr et al [33]	19-22	>1.66 MoM	<1.66 MoM	<0.001 SIG Sensitivity 46% Specificity 90%
Hafner et al [34]	22	1.166	0.983	<0.0001 VHS
N.YU. Et al [15]	22-23	1.52 MoM	1.02 MoM	<0.0001 VHS
Present study	18-23	1.45 MoM	0.95 MoM	<0.0001 VHS Sensitivity 100% Specificity 84.4%

Table 18: Mean gestational age (GA) at delivery: preeclampsia vs. normotensive

Study	Mean GA at	Delivery (Wks)	
	Preeclampsia	Normotensive	P Value
Zhang et al [20]	36	39	<0.05 SIG
MN El Gharib & M Morad [11]	33.83+/-3.19	39.65+/-1.12	0.0001 SIG
Gallo et al [21]	36.4	40.1	<0.05 SIG
Spencer et al [24]	36.2	39.1	0.0001 SIG
Solomon et al [19]	33.8	40.1	<0.0001 VHS
Present study	36.3+/-1.78	39.02+/-0.81	0.007 SIG

Table 19: Mean birth weight: preeclampsia vs. normotensive

Study	Birth weight(kg)		
	Preeclampsia	Normotensive	P value
Zhang et al [20]	2.46	3.27	<0.05 SIG
MN El Gharib & M Morad [11]	1.36+/-699	2.90+/-34	<0.0001 VHS
Gallo et al [21]	2.94	3.44	<0.05 SIG
Spencer et al [24]	2.02	3.41	0.0001 SIG
Present study	2.19+/-0.59	3.01+/-0.26	0.010 SIG

Table 20: Mode of delivery: preeclampsia vs. normotensive

Study	Preeclampsia		Normotensive		
	VD	LSCS	VD	LSCS	P Value
Gupta et al [31]	33.3%	66.7%	78.6%	21.4%	0.001 SIG
Zadeh et al [14]	52%	48%	57%	43%	0.57 NS
Present Study	28.6%	71.4%	57.8%	42.2%	0.149 NS

Table 21: Incidence of early-onset vs. late-onset PE

Study	Normotensive	Early onset	Late onset
Narang s et al [12]	88.46%	7.69%	3.85%
Present Study	86.5%	7.7%	5.8%

Table 22: Preeclampsia - primigravidae vs. multigravidae (individual marker)

Parameter	Preeclampsia			
	Primi(n= 30)		Multi(n=22)	
	N/T	%	N/T	%
Inhibin A (>1.47)	3/30	10%	0/22	0%
Microalbuminuria (>15.2)	9/30	30%	4/22	18%
UACR (>21.5)	3/30	10%	1/22	4.5%
UAPI at 1st trimester (>1.13)	1/30	3.3%	1/22	4.5%
UAPI at 2nd trimester (>1.20)	5/30	16.6%	2/22	9.09%

Conclusion

Prediction of PE remains a challenge even after the identification of a large number of putative biomarkers to predict the pathology. In the present study, we concluded that the women who are prone to develop PE subsequently, had high levels of MAP, UAPI in 1st and 2nd trimester, inhibin A, microalbuminuria and urine albumin to creatinine ratio than the normotensive women. In our setting, MAP, UAPI, inhibin A, microalbuminuria, and UACR markers appeared to be better screening modalities. The biochemical markers are not effective when they are used alone for the prediction of PE. While, the combination of these with the biophysical markers, demographic characteristics, and other novel markers will establish the effective screening models for early prediction of PE. The identification of first trimester markers will contribute to a better understanding of the pathophysiology of PE and will give a clinically validated screening procedure for better management of this disorder.

We cannot come to a very reasonable conclusion from our study because our study conducted in a small group of pregnant women, so to establish the association between biomarkers and occurrence of PE, a further detailed study required in a large group of populations along with measurement of other established markers. Early identification of high-risk cases will offer an opportunity for prophylactic therapy,

such as low- dose aspirin in selected groups of high-risk women screened at risk for PE in the first trimester, thus improve the maternal and perinatal outcome.

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