Original Research Article

Preeclampsia prediction –First trimester screening markers

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A B S T R A C T

Background: Preeclampsia is a multi-system disorder manifested primarily by hypertension and proteinuria during second half of pregnancy. It is a major cause of maternal morbidity and mortality worldwide. Despite decades of research into the condition, the ability of clinicians to predict preeclampsia prior to the onset of symptoms has not improved significantly. In this review we will look at potential biomarkers for early prediction and diagnosis of preeclampsia.

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.

Materials and Methods: This hospital-based prospective observational study conducted on 52 pregnant women, at less than 13 weeks of gestation were recruited. Maternal urine microalbumin, urinary albumin to creatinine ratio, and USG uterine artery PI levels were analyzed among the pregnant women who subsequently developed PE and compare with those who did not develop PE. Methods used for the detection of markers are: immunoturbidimetric method for urine albumin, modified kinetic Jaffe reaction without deproteinization for Urine creatinine and Uterine artery Doppler velocimetry was done by PHILIPS HD11XE transabdominal ultrasound machine using a 4-6 MHz probe with the same sonographer.

Results: In the present study, spot urine microalbumin and spot urine albumin to creatinine ratio (UACR) at 11-13 were significantly higher in women who developed PE subsequently when compared to nonpreeclamptic women.(P<0.0001). The mean levels of 1st and 2nd-trimester uterine artery PI significantly high in women who subsequently developed PE when compared to those who did not develop preeclampsia (P<0.0001). Study results showed a strong association between gestational age at delivery and neonatal outcome (neonatal birth weight and APGAR) with preeclampsia. The maternal urine microalbumin, albumin to creatinine ratio, and uterine artery PI found to have good sensitivity and specificity for early prediction of PE.

Conclusion: Study concluded that the women who are prone to develop PE subsequently, had high levels of MAP, UAPI, microalbuminuria and urine albumin to creatinine ratio than the normotensive women. In our setting, MAP, UAPI, microalbuminuria, and UACR markers appeared to be better screening modalities. The combination of biochemical markers with the biophysical markers, demographic characteristics, and other novel markers will establish the effective screening models for early prediction of PE. 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 in the first trimester, thus improving the maternal and perinatal outcome.

1. Introduction

Preeclampsia is a multisystem disorder characterized by the development of hypertension to the extent of 140/90 mmHg or more, with proteinuria after the 20th week of gestation in a previously normotensive and nonproteinuric

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woman.[1] Hypertensive disorders are the most common medical conditions complicating pregnancy, and they complicate 5 to 10% of all pregnancies worldwide,[2] of which preeclampsia affects 3% to 5% of cases. The incidence of hypertensive disorders of pregnancy in India ranges from 5% to 15% and is associated with 16% of all maternal mortality & 20% of all perinatal mortality in India· Preeclampsia is a major cause of intrauterine growth restriction (IUGR), premature delivery, placental abruption, fetal death, and numerous other adverse pregnancy outcomes. The etiology of preeclampsia remains partly elusive, maladaptive immunological tolerance between maternal, fetal and placental tissues, maternal maladaptation to cardiovascular and inflammatory changes of healthy pregnancy, genetic factors including inherited predisposing genes, and epigenetic influences.[2] Evidence suggests that abnormal placentation is one of the initial events in the pathogenesis of preeclampsia,[3] inadequate trophoblastic invasion of maternal spiral arteries and reduced placental perfusion leads to placental ischemia. Placental hypoperfusion leads to anoxic damage and endothelial dysfunction with the release of inflammatory factors, platelet activation, and abnormal oxidative stress.

Preeclampsia can be early onset (develops before 34 weeks of gestation) or late- onset preeclampsia (develops after 34 weeks of gestation). Early-onset preeclampsia has a higher incidence of adverse outcomes; hence, it is essential to identify pregnancies that are at risk of developing preeclampsia at an early stage for better antenatal care and thus decrease maternal and perinatal mortality.

The rationale for such early identification of high-risk pregnancies is to provide them with more intensive antenatal care and appropriately timed prophylactic therapies with drugs such as low-dose aspirin, which can potentially prevent the development or decrease the severity of the disease.

A combination of maternal risk factors, the uterine artery pulsatility index (PI), mean arterial pressure (MAP), and maternal serum pregnancy-associated plasma protein-A (PAPP-A), placental growth factor (PlGF), PP13, and fetal hemoglobin levels at 11–13 weeks' gestation can be used to identify a high proportion of pregnancies at high risk for early-onset PE.[4–8]

Hence there was a need of affordable test that could permit pre-symptomatic 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.

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).

2. Materials and Methods

Setting: This is a hospital-based prospective observational study conducted at Department obstetrics and gynaecology department, Narayana medical college, and hospital, Nellore, over two years (Oct-2017 to Oct-2019). This study protocol has been approved by the institutional ethical committee of Narayana Medical College and Hospital, Nellore, Andhra Pradesh.

2.1. Inclusion criteria

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

2.2. Exclusion criteria

1. Pregnant women with H/O smoking and alcoholism.
2. Pregnant women with gestational diabetes, overt diabetes mellitus, previous h/o PIH, cardiovascular disease, anemia, and multiple pregnancies.
3. Pregnant women with chronic liver and kidney disease, chronic hypertension (HTN), chronic urinary tract infection, and other chronic diseases.
4. Any maternal or fetal condition that requires termination of pregnancy (congenital malformations like Downs syndrome).
5. Active vaginal bleeding.

After informed written consent, 100 numbers of pregnant women of age 18-40yrs who are less than 13 weeks of gestation attending the obstetrics department fulfilling the inclusion and exclusion criteria recruited into the study. The detailed history, clinical examination, and gestational age confirmed by ultrasonogram. Apart from routine antenatal investigations, other investigations sent related to the present study like urinary microalbuminuria, urine albumin to creatinine ratio, and Doppler USG done. All the enrolled women followed until delivery.

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.

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. Pulsed wave Doppler was used for obtaining three consecutive waveforms, and the pulsatility index (PI) was measured. Blood pressure was

measured at each visit, and mean arterial pressure calculated at mid-trimester.

The variables that were taken in this study are maternal age, parity, BMI, MAP, SBP, DBP(last trimester),microalbuminuria, urine albumin to creatinine ratio(UACR), Uterine artery PI(UAPI) in 1st and 2nd trimester, gestational age at delivery, mode of delivery, neonatal outcome like APGAR and birth weight.

2.3. Statistics

Mean ± SD of all variables calculated for the preeclampsia and normotensive group; the difference was tested using the chi-square test, and Uterine artery PI expressed in Multiples of Median(MoM). The cut-off values, sensitivity, specificity, and predictive values of microalbumin, UACR and UAPI in the 1st and 2nd trimester were analyzed by using Pearson's ROC curve. P value less than 0.05 considered as significant difference. The data obtained were analyzed using IBM SPSS software version 24.0.

3. Results

Among 100 pregnant women, 5 pregnancies were terminated due to lethal congenital anomalies, 6 women had miscarriages, 9 members changed their place of delivery, 4 women developed gestational diabetes, 10 members withdrew their consent in subsequent visits, 2 pregnancies complicated by APH, 4 members landed in a preterm delivery and 8 members were lost follow-up and hence were excluded from the study.

Only 52 members included in the final analysis and followed until delivery. Among them, 45 women remained normotensive, and seven women developed preeclampsia. Out of 7 preeclampsia women, 5(71.4%) members were primigravidae, and 2(28.6%) members were multigravidae, indicating that preeclampsia was more common in primigravidae when compared to multigravidae, (P = 0.429).

The mean age among normotensive pregnant women is 24.18± 4.628 yrs and 23.14±3.436 yrs in the preeclampsia group (P=0.574).

Results shows that the preeclampsia group had a significantly higher BMI than the normotensive group. The preeclampsia group had a significantly higher MAP, higher microalbuminuria level in the first trimester than the normotensive group. Urine albumin to creatinine ratio in the first trimester is higher in the preeclampsia group when compared to normotensive group. The mean uterine artery PI at the first trimester and second trimester was significantly higher in women who developed PE subsequently compared to normotensive group(Table 1).

The mean gestational age at delivery in the preeclampsia group is 36.35+/-1.78 weeks, and in normotensive women is 39.02+/-0.81 weeks (P= 0.007). It indicates that the average gestational age at delivery in the preeclampsia group was significantly lower than that in the normotensive group.

Among normotensives, 26(57.8%) members had normal vaginal delivery, and 19(42.2%) members underwent LSCS. Out of 7 preeclampsia women, 2(28.6%) women delivered vaginally, and 5(71.4%) members had LSCS. It shows that there was no significant difference between the preeclampsia group and normotensive pregnant women concerning the mode of delivery (P= 0.149).

The average newborn birth weight in the preeclampsia group was significantly lower than that in the normotensive group and the APGAR at 1st and 5th min was lower in the preeclampsia group when compared to the normotensive group with significant p value-<0.0001 and 0.016.

75% of primigravida and 25% of multigravida had early onset preeclampsia and corresponding figures of late onset preeclampsia were 66.7% and 33.3% respectively. It indicates there was no statistically significant difference between the onset of preeclampsia in primigravidae and multigravidae (p value-0.714).

The MAP in primigravidae is 90.78+/-8.77 mm of Hg and in multigravidae is 88.07+/-6.58 mm of Hg, indicates that there was no statistically significant difference in MAP (p-value 0.229).

The mean microalbuminuria in primigravidae was 14.16+/-8.11 mg/l and in multigravidae was 16.05+/-23.45 mg/l, which indicates that there was no significant difference in microalbuminuria (p-value 0.719).

The mean urinary albumin to creatinine ratio in primigravidae was 15.60+/-6.14 mg/g and in multigravidae was 13.80+/-10.67 mg/g, which indicates that there was no significant difference in albumin to creatinine ratio (p-value-0.447).

The first-trimester uterine artery PI in primigravidae was 0.98+/-0.22 MoM and in multigravidae was 1.04+/-0.30 MoM, which indicates that there was no significant difference in first-trimester uterine artery PI between primigravidae and multigravidae with (p-value- 0.405) and the corresponding figures in second-trimester uterine artery PI were 1.01+/-0.30 MoM and 1.02+/-0.28 MoM respectively, which indicates that there was no statistically significant difference in second-trimester uterine artery PI between primigravidae and multigravidae with p-value-0.953.

The optimum cut off value for spot urinary albumin to creatinine ratio to predict preeclampsia was 21.5. The value in our study was 27.67+/-11.60 (p value <0.0001 VHS)with sensitivity of 85%, the specificity of 91%, PPV of 60%, and NPV of 97.62%.

The cut-off value for random microalbuminuria to predict preeclampsia was 15.2. The value in our study was 40.48+/-31.81(p value 0.049 SIG) which had a sensitivity of 100%, the specificity of 71%, PPV of 35%, and NPV of 100%.

Table 1: Mean maternal risk factors in normotensive vs. preeclampsia

Variable	Normotensive (n=45) (mean± sd)	Preeclampsia (n=7) (mean± sd)	t- value	p-value
maternal age	24.18+/-4.628	23.14+/- 3.436	0.566	0.574 NS
Mean BMI (kg/m^2)	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
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 at 2 nd trimester (MoM)	0.95+/-0.24	1.45+/-0.17	-5.210	<0.0001 (VHS)
Mean gestational age at delivery(wks)	39.02+/-0.81	36.35+/-1.78	3.901	0.007 SIG

NS= not significant, VHS- Very high significant, SIG- Significant

Table 2: Newborn parameters in normotensive group vs. preeclampsia group

Variable	Normotensive (n=45) (mean+/- SD)	Preeclampsia (n=7) (mean+/- SD)	t- value	p-value
Meanbirth weight (B.WT) (kg)	3.016+/-0.26	2.19+/- 0.59	3.580	0.010 (SIG)
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

VHS- Very high significant; SIG- Significant

Table 3: Early onset versuslate onset PE- Primigravida vs Multigravida

Parity	Early onset PE	Late onset PE
Primi	3	2
	75%	66.7%
Multi	1	1
	25%	33.3%

Chi-square value = 0.674, P Value = 0.7147 (Not Sig.)

Table 4: Cut off value, sensitivity, specificity, positive predictivevalue (PPV), and negative predictive value (NPV) of markers

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

The cut-off values of first-trimester uterine artery Doppler PI to predict the preeclampsia is >1.13 MoM. The value in our study 1.3+/-0.20(p value <0.0001(VHS) which had a sensitivity of 71%, the specificity of 95%, PPV of 71% and NPV of 95%. The area under the curve for PI in the first trimester is 0.946.

The cut-off values for uterine artery Doppler PI in the second trimester to predict preeclampsia is >1.20 MoM. The value in our study was 1.45+/-0.17 MoM (p value<0.0001) which had a sensitivity of 100%, the specificity of 84%, PPV of 50% and NPV of 100%. The area under the curve for PI in the second trimester is 0.954.

4. Discussion

The definitive pathophysiology of preeclampsia is not known. There is proof that increased proliferation of the underlying cytotrophoblast in preeclampsia, 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 increased levels of certain biophysical and biochemical markers.

The incidence of PE worldwide ranges from 5-7% of pregnancies, and in India, the prevalence ranges from 8-10%. In the present study, out of 52 pregnant women,

seven members developed preeclampsia subsequently with the incidence of 13.4%.[8–12]

Maternal age is one of the most important risk factors associated with pregnancy-related hypertensive disorders. Young women of less than 20years and women over 35 years are found to be more prone for the development of Preeclampsia.[13–15]

PE is twice as common in primigravida women as compared to multigravida. The present study shows increased incidence of PE in primigravidae when compared to multigravidae in par with the studies done by Poon et al., and Akolekar et al., showing that the incidence of preeclampsia are significantly more in primigravidae.[16,17] Whereas a study done by Sharma et al. shows the incidence of PE was more in multigravidae.[18]

The risk of preeclampsia was more in obese patients, and the risk doubles with each 5 to 7 kg/m^2 increase in prepregnancy BMI. Obesity is associated with renal hyperfiltration, hyperperfusion, glomerular hypertrophy and diabetes-like changes including focal mesangial sclerosis or glomerular and tubular basement membrane thickening.[9,10,19] In our study also preeclampsia was noted in women with high BMI(30kg\m^2).

In PE, the possible mechanism for the disturbed invasion is hardening and structural abnormality of the vessel wall. Hardening of blood vessel walls might be provoked by persistent high blood pressure. In pregnancies that develop PE, MAP at 22-24 weeks gestation is higher than the normal pregnancies, and the increase is inversely related to the gestational age at delivery.[20,21] Studies done by Gallo et al., and Jaldli et al., show the midtrimester MAP was significantly higher in the preeclampsia group when compared to the normotensive group and the present study is in accord with the above studies with significant p value<0.001.

Persistent microalbuminuria indicates a high probability of damage to the glomerular functional capacity of the kidney. Increased levels of microalbuminuria in early pregnancy can be used as a predictor of PE. Studies by Inder Pal et al., Sharawy et al., shown that the mean microalbuminuria levels in early pregnancy are significantly higher in women who subsequently developed preeclampsia than those who did not develop preeclampsia later.[22,23] In the present study, the sensitivity and specificity of urinary microalbuminuria for the prediction of PE were 100% and 71%, respectively showing urinary microalbuminuria is a better sensitive marker for the prediction of PE.

The studies done by Poon et al., Upadhyay A et al., Devi LT et al., and Gupta et al. showed that the URINE ALBUMIN TO CREATININE RATIO(UACR) values were significantly higher in the preeclampsia group when compared to the normotensive group with significant p-value.[24–26] In the present study, the sensitivity and specificity of spot urine albumin to creatinine ratio in the prediction of preeclampsia was 85% and 91%, respectively. Therefore, the spot UACR may be helpful to predict early onset preeclampsia.

In pregnancies destined to develop PE have raised placental vascular resistance, which is detected in uterine artery Doppler ultrasound in the form of increased pulsatility index. In the studies done by Narang et al., uterine artery PI at 11-14 weeks of gestation was found to be the best parameter for screening women prone for developing PE. In studies done by Elisa Ilubra et al., Hafner et al., showed the mean second trimester uterine artery PI was significantly higher in the preeclampsia group when compared to normotensive group. Our study also has shown high values in both first trimester and second trimester mean uterine artery PI in the preeclampsia group when compared to normotensives with high sensitivity and specificity along with significant p-value. On the whole second trimester uterine artery PI seems to be a more sensible marker for the prediction of early onset PE.(100% specificity).

Early-onset PE (also known as "placental PE") results from impaired trophoblast invasion into the spiral arteries, leading to placental ischemia and oxidative stress. Placental histology in early-onset PE demonstrates thrombotic changes in the villous tree. Late-onset PE ("maternal PE") is considered to be secondary to the maternal cardiovascular and metabolic predisposition for endothelial dysfunction. Study done by Narang et al. shows that 11.54% of pregnant women developed PE. Among them, 7.69% developed early-onset PE, and 3.85% developed late-onset PE.[10] The present study shows consistent findings in par with the above study, 7.7% developed with early-onset PE and 5.8% developed with late onset PE with significant p value.

Delivery is the definitive management of preeclampsia depending upon its severity. The mean gestational age at delivery is significantly lower in the preeclampsia group when compared to the normotensive group. A positive correlation found between neonatal birth weight and the time of development of PE. There is a difference between near- term PE(late onset preeclampsia) without demonstrable fetal involvement and early onset PE associated with low birth weight and preterm delivery. In severe PE before 34 wks, fetus is usually growth restricted and induction of labor is invariably being unsuccessful, leading to high probability of operative delivery. Gupta et al. shows the Cesarean section rate is significantly higher in the preeclampsia group when compared to the normotensive group.[27] (p value 0.001). But as per Zadeh et al., there was no significant difference observed in type of delivery between Preeclampsia and normotensive groups. Our study findings found to be consistent with Zadeh et al., study showing no statistically significant difference between two groups (p value 0.149).

As per our study figures, with a cut off value >15.2 for microalbuminuria, 30% of primigravidae and 18% of

multigravidae developed PE.

At a cut-off value of >21.5 for UACR, 10% of the primigravidae and 4.5% of multigravidae developed PE.

At a cut-off value >1.13 for UAPI in first trimester, 3.3% of the primigravidae and 4.5% of multigravidae and for uterine artery PI in second trimester with a cut-off value>1.20, 16.6% of the primigravidae and 9.09% of multigravidae developed PE. Second trimester Uterine artery PI appears to be a more sensitive marker.

In the present study, we did a step further by considering the cut-off value to various markers and to find out whether markers influence the parity for the development of PE. With the same cut-off values, the incidence of PE in primigravidae is higher when compared to the multigravidae. So, this raises a point to detect the factors which are preventing PE in multigravidae. A search for those protecting factors in the multigravidae which might be helpful in the future to mark the presence/absence of the same in a primigravidae to pin-point her future vulnerability to the development of PE.

5. Conclusion

Prediction of PE remains a challenge even after the identification of a large number of putative biomarkers to predict the pathology and its onset. The present study concluded to a reasonable extent that the women who are prone to develop PE subsequently, had high levels of MAP, UAPI (in 1st and 2nd trimester), microalbuminuria and urine albumin to creatinine ratio than the normotensive women. In our setting, MAP, UAPI, microalbuminuria, and UACR markers appeared to be better screening modalities for early prediction of PE.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

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