

TITLE: Microalbuminuria and spot protein creatinine ratio in early pregnancy as a predictor of preeclampsia: A prospective observational study

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Running title:-

First trimester Microalbuminuria and spot PCR levels in preeclampsia

Microalbuminuria and Spot protein creatinine ratio in early pregnancy as a predictor of preeclampsia: A prospective observational study
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ABSTRACT:-

Introduction:- Hypertensive disorders complicate 5-10% of all the pregnancies and preeclampsia is identified in 3.9%⁽²⁶⁾. Preeclampsia is a pregnancy specific syndrome characterized by the development of hypertension and proteinuria in the second trimester of the pregnancy. Microalbuminuria and elevated spot protein creatinine ratio are commonly found in preeclampsia.

The aim of this study was to determine microalbuminuria and spot creatinine ratio in early pregnancy as predictors of pre-eclampsia.

Methods:- The study was conducted among 102 pregnant women by detecting the levels of albuminuria and spot protein creatinine ratio at 10-14 weeks period of gestation. Random urine sample of about 5 ml was taken to analyse the samples for microalbuminuria and spot protein creatinine ratio. All the women included in the study were followed up till delivery to rule out the possibility of developing preeclampsia depending on their microalbumin and spot protein creatinine ratio values.

Results:- Pregnant women who developed preeclampsia or eclampsia had significantly higher levels of microalbumin and spot protein creatinine ratio.

Conclusion:- A detailed study among a larger group of population is required to determine that microalbuminuria and spot protein creatinine ratio in early pregnancy are definitive predictors of preeclampsia.

Keywords:- Microalbuminuria, Spot protein creatinine ratio, Preeclampsia, Pregnancy.

Introduction:-

Preeclampsia is a pregnancy specific syndrome defined as the new onset of hypertension and proteinuria during the second trimester or a new onset of hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation in a previously normotensive woman ⁽¹⁾. The incidence of preeclampsia in nulliparous women ranged from 3-10% and for multiparas it is lesser than that ⁽¹⁾. It is a potentially dangerous pregnancy complication with about 1million cases being registered in India per year. In Indian scenario, the incidence of preeclampsia is 5.47% in primigravidae and 2.8% in multigravidae .

However, there is no gold standard method for diagnosing preeclampsia apart from it being characterized by the triad of hypertension, proteinuria and edema in the 2nd trimester. The presence of proteinuria in preeclampsia patients suggests that detection of microalbuminuria and elevated protein creatinine ratio in 1st trimester could be a predictor for development of preeclampsia in various studies conducted ^(2,3,4,5,6) .

Microalbuminuria is defined as a moderate increase in the level of urinary albumin excretion above normal levels in the absence of clinically detectable nephropathy ^(8,9,10) . Persistent microalbuminuria indicates endothelial dysfunction and a high probability of damage to the glomerular filtration capacity of the kidney, which is a great diagnostic relevance in pregnancy as a possible predictor for developing preeclampsia⁽²⁾ .Microalbuminuria is noted to be present if urinary microalbumin levels are within the range of 30-300mg/L ⁽⁷⁾.

Abnormal protein excretion is defined as spot protein creatinine ratio ≥ 0.3 or persistent 30mg/dl protein in a random urine sample ⁽¹⁾. Spot protein creatinine ratio is used as an easy alternative to 24hr urinary protein as the later is time consuming, collection is cumbersome, inconvenient to the patients and subject to errors such as incomplete collection leading to inaccuracies in 13-68% of the collections ⁽¹³⁾. There are studies that show strong association between random protein-creatinine ratio and 24 hour urinary protein excretion, the international society for the study of hypertension in pregnancy has accepted this test as a method for identifying

significant proteinuria ⁽¹⁴⁾. This suggests that microalbuminuria and elevated spot protein creatinine ratio in early pregnancy could predict preeclampsia.

Objectives:-To investigate the role of microalbuminuria and elevated spot protein creatinine ratio in early pregnancy and its relation with development of preeclampsia.

Methodology:- It is a prospective study conducted at Rajarajeswari medical college and hospital over a period of 9 months (February 2019-October 2019), Bengaluru after obtaining permission from the institute's ethical committee. Random urine samples were taken from 102 pregnant women who attended antenatal checkups in their first trimester in order to detect the levels of albumin and spot protein creatinine ratio at 10-14 weeks period of gestation to analyse the development of preeclampsia till delivery.

Exclusion criteria:-

1. Known cases of hypertension, diabetes mellitus and renal disorders
2. Multiple gestation
3. History of preeclampsia/eclampsia in previous pregnancies.
4. History of renal surgeries in the past.
5. Women with symptoms of UTI

Inclusion Criteria:- Pregnant women at 10-14 weeks period of gestation.

1. Informed written consent taken for all the subjects
2. A detailed obstetric and menstrual history taken by following a pre-designed data sheet
3. General, systemic and obstetric examination carried out on the same day.

4. These patients will be under regular follow-up till the date of delivery.
5. Specific note will be made of the development of preeclampsia during gestational period and/or at the time of delivery.

10ml of venous blood was collected from each subject for a routine antenatal blood check-up to rule out diabetes, renal diseases and hyperlipidemia.

All the selected subjects during their 10-14 weeks period of gestation, gave their clean catch of urine sample(5ml) in a container after which the necessary biochemical tests were performed.

Urine analysis:-

1. Estimation of microalbuminuria by microalbumin-turbilatex method, a quantitative turbidimetric test for the measurement of microalbumin in human urine. The samples collected are adjusted to a pH at 7.0 with NaOH/HCL 1mol/L. Sodium azide 1g/L is added to prevent contamination. The urine is then centrifuged before testing. Calibration: The sensitivity of the assay and target value of the calibrator have been standardized against the international reference material CRM 470/RPPHS. Calculation:- Microalbuminuria concentration (mg/L)=(A2-A1) sample/ (A2-A1) calibrator.
2. Estimation of total urine protein(calorimetric test): Urine is collected by standard procedures. Volume is measured and stored at 2-8 degree Celsius. Calculation: A(sample) x 1000(standard concentration) x volume. (L) urine 24hr= mg protein/24hrs.

3. Estimation of urine creatinine (creatinine enzymatic): Random urine sample is collected and the exact volume is measured. It is diluted in 1+19 ratio with distilled water and the results are multiplied with 20. Calculation: The results are automatically calculated by the instrument.

Once the results were obtained, the subjects were followed up to delivery and the possibility of developing preeclampsia was observed with respect to their albumin and spot protein creatinine ratio values. The subjects were diagnosed with preeclampsia when they developed hypertension and proteinuria from second trimester onwards. The cut off value for microalbuminuria was taken as 30-300mg/L and ≥ 0.3 for elevated spot creatinine ratio. The collected data were expressed as mean \pm SD.

Statistics:- The collected data were analysed with IBM.SPSS statistics software 23.0 Version .To describe about the data, descriptive statistics, frequency analysis & percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Independent groups the Unpaired sample t-test was used.To find the significance in categorical data Chi-Square test was used. In both the above statistical tools the probability value < 0.05 is considered as significant level.

Results:- A total of 102 samples were collected during the study, out of which 29 subjects remained normotensive till delivery. Remaining 73 subjects developed preeclampsia(Table 3).

Their mean systolic BP was 149.3 ± 13.6 mmhg and diastolic BP was 93.8 ± 7.4 mmhg, microalbumin level was 50.2 ± 25.4 and spot protein creatinine ratio was 0.5 ± 0.5 respectively(Table 1). Out of 40 cases with microalbuminuria in early pregnancy, 28 cases had developed preeclampsia which is and out of 20 cases with elevated spot protein creatinine ratio, all the 20 had developed

preeclampsia. Only 1 case with completely normal values during early pregnancy had developed preeclampsia.

Pregnant women who developed preeclampsia were having significantly higher microalbumin levels and spot protein creatinine ratios when compared to normotensive pregnant women.

No statistical significance was observed when parity, age and their association with development of preeclampsia were studied in this study (Table 1, 2).

The statistical significance of age, microalbuminuria, spot protein creatinine ratio and mean blood pressure values have been summarised (Table4).

Discussion:- In our study, we have taken 102 pregnant women and have found out that the levels of microalbumin and spot protein creatinine ratio were significantly higher in women who developed preeclampsia later in pregnancy. Various studies have been conducted so far to see the association of spot protein creatinine ratio, microalbuminuria and development of preeclampsia. Inder pal kaur et al had reported that microalbuminuria and elevated albumin-creatinine ratio were having higher statistical significance in predicting preeclampsia ⁽¹⁷⁾. Similarly, K.Fatema et al had also reported in their study that patients with microalbuminuria developed preeclampsia eventually ⁽¹⁶⁾. In another study Fady S. et al had reported that, albumin creatinine ratio is significantly higher in patients with severe preeclampsia than in those with mild form of the disease ⁽¹⁸⁾. The presence of microalbuminuria in some otherwise symptom free patient confirms that changes in renal function are present in patients in whom preeclampsia will eventually develop, suggesting that early pregnancy levels of microalbuminuria can be used as predictors of preeclampsia with high negative predictive value ⁽⁷⁾.

Salako et al found that microalbuminuria might be a good predictor of preeclampsia with high sensitivity but a low positive predictive value ⁽²⁰⁾. It is clearly understood that there is need for more detailed studies in order to establish the usefulness of microalbuminuria and spot protein creatinine ratio in predicting preeclampsia.

Conclusion:- This study was conducted on a smaller population of pregnant women, so a detailed study to assess the association of preeclampsia with early pregnancy microalbuminuria and elevated spot protein creatinine ratio along with the other established markers is needed.

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Disclosure of interests:

There was no conflict of interest among the authors, no relevant financial, personal, political, intellectual and religious interests.

Contribution to authorship:

Dr.Rupakala B.M came up with the idea of conducting a research on early diagnostic markers or predictors of preeclampsia/eclampsia. With her amount of knowledge and experience in the field of obstetrics & gynaecology, she wanted to make a contribution to preventive health care among pregnant women, predicting and preventing preeclampsia being one. After collecting data from various studies and published articles, she proposed the idea of conducting a prospective

observational study based on first trimester spot protein creatinine ratio, microalbuminuria and its association with development of preeclampsia/eclampsia. Dr.G.Sai Sudha collected the samples, secured the reports and followed the patients up till delivery personally. The study was thoroughly revised and regularly monitored under the guidance of Dr.Rupakala B.M.

Ethics approval:-

Ethical approval was not necessary for this study as it was only an observational study with absolutely no intervention.

Funding:-

No funds were required for this study as all the sample collection from the cases and sample processing in the laboratory were done free of cost at our institution.

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