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Research Article

Renal markers in normal and hypertensive disorders of pregnancy in Indian women: a pilot study

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ABSTRACT

Background: Altered renal function is an essential component of the pathophysiological process in pre-eclampsia. Kidneys play an important role in the turnover of low molecular weight substances such as creatinine, uric acid and cystatin C. The present study was undertaken if these serum markers were characteristically altered in Indian pregnant women.

Methods: Serum levels were therefore determined in samples from 69 healthy women at term as well as in 27 samples of patients with Pregnancy induced hypertension (PIH) and in 20 patients with pre-eclampsia (PE).

Results: The levels of all three components were significantly higher in pre-eclamptic patients when compared to healthy controls with the mean \pm SD being 1.47 ± 0.9 vs. 1.06 ± 0.2 for cystatin C, 0.95 ± 0.2 vs. 0.67 ± 0.1 for creatinine and 6.13 ± 1.8 vs. 4.28 ± 1.1 for uric acid respectively. In PIH cystatin C was significantly higher, 1.25 ± 0.9 unlike creatinine, 0.67 ± 0.14 and uric acid, 4.30 ± 1.0 . Receiver operating characteristic (ROC) plots demonstrated that the diagnostic accuracy of serum creatinine was superior to serum uric acid and serum cystatin C and serum uric acid was better than serum cystatin C.

Conclusion: The maternal serum cystatin C, creatinine and uric acid were all significantly elevated at the end of pregnancy in pre-eclampsia compared to those of healthy pregnant women. If this rise in the above markers during early pregnancy could predict the onset of PIH/PE, needs to be investigated.

Keywords: Pregnancy, Pregnancy induced hypertension, Pre-eclampsia, Cystatin C, Creatinine, Uric acid

INTRODUCTION

Pre-eclampsia is a complex and serious multi-system disorder of human pregnancy with a worldwide incidence of 5-7% and contributes significantly to maternal and perinatal morbidity and mortality.^{1,2} It is characterized by hypertension, proteinuria, and a generalized systemic vasoconstriction arising from circulatory disturbances secondary to a generalized endothelial dysfunction caused by inflammation.³ It is associated with defective endovascular trophoblastic invasion and insufficient remodeling of the uterine spiral arteries.^{4,5,6,7} Altered renal function is an essential component of the pathophysiological process in pre-eclampsia and close

monitoring of renal function is important to ensure a timely delivery before serious renal damage occurs. The turnover of most of the low molecular weight substances such as creatinine, uric acid and cystatin C occur by the kidneys. Serum cystatin C is an endogenous marker of renal function. It is synthesized by all nucleated cells, produced at a constant rate and is exclusively eliminated from the circulation by glomerular filtration. Several studies have shown that serum cystatin C is a better marker for glomerular filtration rate than serum creatinine^{8,9} particularly for individuals with small to moderate decrease in glomerular filtration rate, but only few studies^{10,11,12,13,14} of serum cystatin C in pre-eclampsia. However, there are no Indian studies

to evaluate the relationship between serum cystatin C and pre-eclampsia. Hence, we would like to compare serum cystatin C, creatinine and uric acid in normal and hypertensive disorders of pregnancy (PIH and PE). We hypothesize that a significant difference exists between the three renal markers in Indian pregnant women and also serum cystatin C is a better marker than serum creatinine and serum uric acid.

METHODS

Non fasting venous blood samples (5 ml) were obtained from 69 healthy pregnant women at term (gestational age > 37 weeks) admitted to the labor ward at the Department Of Obstetrics & Gynecology, Medciti Institute Of Medical Sciences, Ghanpur, Ranga Reddy district, Andhra Pradesh, India. We included only healthy women without present or past history of hypertension, diabetes mellitus or clinically detected renal disease. We also acquired venous blood samples consecutively from 27 women with PIH and 20 pre-eclamptic women during the last trimester and got admitted for delivery. The criteria for diagnosing pregnancy induced hypertension and pre-eclampsia were based on the classification and diagnosis of the hypertensive disorders of pregnancy: statement from the international society for the study of hypertension in pregnancy (ISSHP).¹⁵ Pregnancy induced hypertension is defined as the development of hypertension (systolic blood pressure \geq 140 mmHg and or a diastolic blood pressure \geq 90 mmHg) for the first time after mid pregnancy. Pre-eclampsia is defined as the development of hypertension (systolic blood pressure \geq 140 mmHg and or a diastolic blood pressure \geq 90 mmHg) for the first time after mid pregnancy and urinary albumin excretion 1+ (30mg/dl). These patients were also previously healthy without underlying renal disease, essential hypertension or diabetes. 10 ml of early morning or random midstream urine was collected for analysis of urine proteins in all included participants. National Committee for Clinical Laboratory Standards (NCCLS) Guidelines^{16, 17} was followed for sample collection, handling and processing. Serum creatinine and uric acid were analyzed immediately and the rest of the serum sample was appropriately labeled and stored at -80°C until analysis for cystatin C. Written informed consent was taken from all included participants. A study proforma was used to collect information on maternal sociodemographic, medical characteristics and delivery outcomes from the medical records.

Measuring parameters- Maternal

Height and weight of the patient at the time of admission for delivery were recorded using a calibrated measuring scale (SECA). The international society for the study of hypertension in pregnancy guidelines¹⁵ were followed for the measurement of blood pressure. Two measurements were taken 4 hours apart with an oscillometric digital sphygmomanometer (Model: Omron HEM-780N3).

Serum cystatin C was measured by a fully automated particle-enhanced immunonephelometric assay (N Latex cystatin C, Dade-Behring, Inc) in BN Pro-Spec nephelometer (Dade Behring, Inc, Deerfield, IL) according to the manufacturer's instructions.¹⁸ Polystyrene particles coated with specific antibodies to cystatin C are aggregated when mixed with samples containing human cystatin C. These aggregates scatter a beam of light passed through the sample. The intensity of the scattered light is proportional to the amount of cystatin C in the sample. The result is evaluated by comparison with a standard of known concentration. The assay range is 0.23 to 8.0 mg/L. The reference range for young, healthy persons is reported to be 0.53 to 0.95 mg/L. The inter-assay coefficient of variation using controls level 1 and level 2 with assigned values of 0.92 mg/L and 1.8 mg/L were 2.2% and 1.0% respectively.

Serum creatinine was measured by modified kinetic Jaffe's reaction in Dade Behring-Dimension Xpand plus system using creatinine flex reagent cartridge according to the manufacturer's instructions.^{19, 20} The assay range is 0-20 mg/dl. The reference range for young, healthy females is reported to be 0.6-1.0 mg/dl. The inter-assay coefficient of variation using Bio-Rad controls, level 1 and level 2 with assigned values of 2.16 mg/dl and 6.39 mg/dl were 3.7% and 3.6% respectively.

Serum uric acid was measured by modified Uricase method in Dade Behring-Dimension Xpand plus system using uric acid flex reagent cartridge according to the manufacturer's instructions.^{21,22} The assay range is 0-20 mg/dl. The reference range for young, healthy females is reported to be 2.6- 6.0 mg/dl. The inter-assay coefficient of variation using Bio-Rad controls, level 1 and level 2 with assigned values of 4.89 mg/dl and 9.03 mg/dl were 4.4 % and 4.4 % respectively.

An early morning or random mid-stream urine sample was collected for estimation of proteins. The concentration of total proteins in urine was measured by semi-quantitative dip stick method.²³ Two readings of 1+ (30 mg/dl) is diagnostic of pre-eclampsia.

Measuring Parameters- Fetal

The weight of the newborn was recorded by a digital weighing scale (SECA 354/364).

Statistical Analysis

The data was entered in a MS-Excel database. After cleaning and validation, the data was analyzed using the statistical program MedCalc for PC, version 12.7.0 (MedCalc Software, Belgium). The analysis was divided into two parts, initially descriptive analysis for intergroup comparisons and later to determine the cut – off levels for maximal sensitivity and specificity for serum levels of cystatin C, creatinine and uric acid; Receiver operating characteristic (ROC) plots was used. Inter group comparisons were done using one way ANOVA and post

hoc analysis by Student-Newman-Keuls test. A p - value of < 0.05 was considered as statistically significant.

RESULTS

The height of 16 patients (11 controls, 4 PIH, 1 PE) and the weight of 8 patients (7 controls, 1 PIH) were not available. There was no statistically significant difference in the mean values of maternal age, height, weight and

parity status but we found a statistically significant difference (p < 0.05) in the mean values of BMI, systolic blood pressure, diastolic blood pressure, urinary proteins gestational age of delivery, mode of delivery, birth weight (Table: 1), serum cystatin C, serum creatinine and serum uric acid between the three study groups (Table 2). Post hoc analysis revealed that the mean values of serum cystatin C, creatinine and uric acid were significantly higher in patients with pre-eclampsia when compared to healthy pregnant women.

Table 1: Maternal & child characteristics in the study groups, MediCiti Institute of Medical Sciences, Hyderabad, 2012.

Parameters	Healthy controls (n= 69)			PIH (n=27)			Pre-eclampsia (n = 20)			P value
	Mean (SD)	95% CI	N (%)	Mean (SD)	95% CI	N (%)	Mean (SD)	95% CI	N (%)	
Age (Years)	21.6 (2.5)	20.9 to 22.2		21.4 (2.2)	20.5 to 22.3		21.1 (1.9)	20.2 to 22.0		0.75
Height (cm)	153.0 (5.5)	151.6 to 154.5		152.8 (5.3)	150.5 to 155.1		154.4 (5.9)	151.4 to 157.4		0.61
Weight (Kg)	54.3 (9.3)	51.9 to 56.7		57.6 (9.2)	53.8 to 61.4		57.9 (7.7)	54.2 to 61.6		0.16
BMI	22.9 (2.8)	22.1 to 23.6		25.0 (3.3)	23.6 to 26.4		24.2 (2.6)	22.8 to 25.5		0.01*
Systolic blood pressure (mmHg)	114.1 (8.9)	112.0 to 116.3		150.7 (9.1)	147.1 to 154.3		162.0 (14.7)	155.1 to 168.8		< 0.001*
Diastolic blood pressure (mmHg)	77.7 (7.6)	75.9 to 79.6		101.1 (8.0)	97.9 to 104.2		106.0 (6.8)	102.8 to 109.1		< 0.001*
Primigravida (%)			38 (55.1)			18 (66.7)			16 (80)	0.13
Mode of delivery										0.02*
Normal vaginal delivery			45 (65.2)			17 (62.9)			8 (40)	
Instrumental delivery			11 (15.9)			3 (11.1)			3 (15)	
LSCS emergency			10 (14.4)			5 (18.5)			9 (45)	
LSCS elective			3 (4.3)			2 (7.4)			0 (0)	
Urine proteins										< 0.001*
Nil			67 (97.1)			6 (22.2)			1 (5)	
Trace			2 (2.8)			21 (77.7)			1 (5)	
1+			0 (0)			0 (0)			12 (60)	
2+			0 (0)			0 (0)			6 (30)	
3+ and above			0 (0)			0 (0)			0 (0)	
Gestational age of delivery (weeks)	38.7 (1.5)	38.3 to 39.1		38.1 (1.4)	37.5 to 38.7		36.9 (4.0)	35.0 to 38.8		0.007*
Birth Weight (Kg)	2.7 (0.4)	2.6 to 2.8		2.6 (0.4)	2.4 to 2.8		2.3 (0.8)	2.0 to 2.7		0.02*

* Statistically Significant (P < 0.05)

ROC curves²⁴ were used to compare the diagnostic potential of serum cystatin C, creatinine and uric acid as renal markers in hypertensive disorders of pregnancy. It shows that serum creatinine had a superior diagnostic

accuracy for preeclampsia compared to that of serum uric acid or serum cystatin C and that the diagnostic accuracy of serum uric acid was better than that of serum cystatin C (Table: 3, fig: 1). There was no difference in the AUC between the three markers in those who developed PIH.

Table 2: Mean values of S-cystatin C, S-creatinine and S-uric acid in the study groups, MediCiti Institute of Medical Sciences, Hyderabad, 2012.

Parameters	Healthy controls (n= 69)		PIH (n=27)		Pre-eclampsia (n = 20)		P value
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	
Serum cystatin C (mg/L)	1.06 (0.2)	1.01 to 1.12	1.25 (0.9)	0.86 to 1.64	1.47 (0.9)	1.01 to 1.92	0.04*
Serum creatinine (mg/dl)	0.67 (0.1)	0.64 to 0.69	0.67 (0.14)	0.62 to 0.73	0.95 (0.2)	0.82 to 1.08	< 0.001*
Serum uric acid (mg/dl)	4.28 (1.1)	4.00 to 4.57	4.30 (1.0)	3.87 to 4.72	6.13 (1.8)	5.26 to 7.00	< 0.001*

* Statistically Significant (P < 0.05)

Table 3: ROC analysis of renal markers in hypertensive disorders of pregnancy, MediCiti Institute of Medical Sciences, Hyderabad, 2012.

	PIH					Pre-eclampsia				
	AUC (95% CI)	Sensitivity	Specificity	+LR	-LR	AUC (95% CI)	Sensitivity	Specificity	+LR	-LR
Serum cystatin C (mg/L)	0.50 (0.39 to 0.60)	66.67	44.93	1.21	0.74	0.65 (0.54 - 0.75)	50.0	87.0	3.83	0.58
Serum creatinine (mg/dl)	0.51 (0.41 to 0.62)	22.22	92.75	3.07	0.84	0.85 (0.76 - 0.91)	65.0	97.1	22.42	0.36
Serum uric acid (mg/dl)	0.53 (0.42 to 0.63)	74.07	42.03	1.28	0.62	0.80 (0.70 - 0.88)	75.0	76.8	3.23	0.33

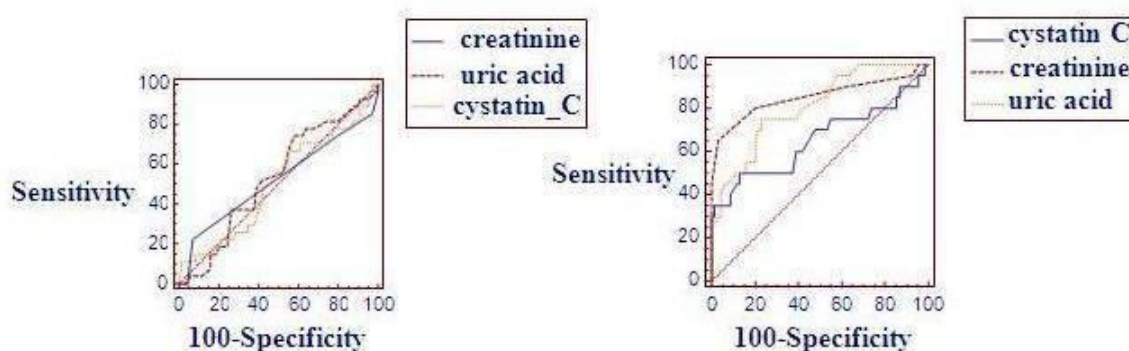


Figure 1: Comparison of ROC curves for serum creatinine, serum uric acid and serum cystatin C in PIH and pre-eclampsia respectively.

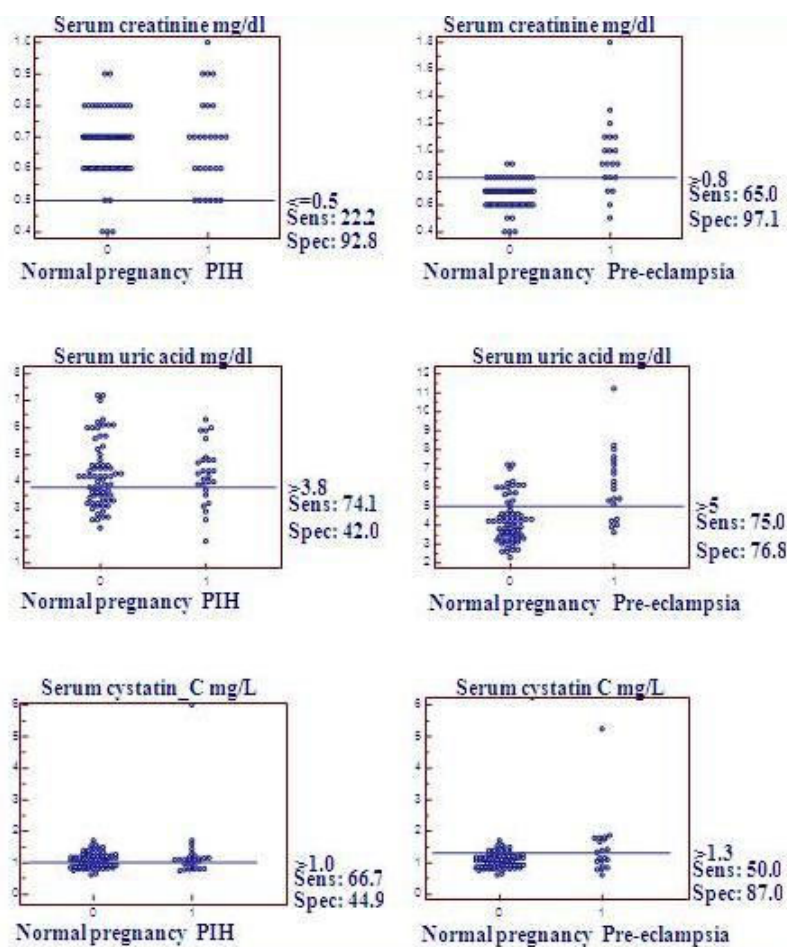


Figure 2: Levels of serum cystatin C, serum creatinine and serum uric acid in preeclampsia and normal pregnancy, in PIH and normal pregnancy given in mg/L and mg/dL respectively, with calculated cut-off levels for maximal sensitivity and specificity.

DISCUSSION

The renal dysfunction occurring in hypertensive disorders of pregnancy can be due to hemodynamic changes,¹² glomerular endotheliosis,²⁵ as well as podocyte damage.²⁶ It is characterized by a decline in GFR, the values of which can be above normally expected values in healthy non-pregnant women due to altered hemodynamics in pregnancy. It is therefore necessary to closely monitor renal function so that prompt therapy can be implemented in order to prevent further renal damage. The most widely used markers of renal function in women with hypertensive disorders are serum concentrations of cystatin C, creatinine and uric acid.

Several international studies have been done on serum cystatin C levels in normal pregnancy and pre-eclampsia.^{10,11,12,13,14,27,28} Serum cystatin C is a marker for glomerular filtration rate (GFR) in non pregnant healthy women below 50 years of age²⁹ and also during pregnancy.^{30,31} Although glomerular filtration rate, defined as the plasma clearance of low molecular weight substances, is normally increased during pregnancy^{32,33} expecting a decrease in serum cystatin C, it does not normally decrease during pregnancy. This might be due

to increased production of cystatin C during pregnancy due to an increased number of nucleated cells. We have found significantly elevated levels of serum cystatin C in twin pregnancies, which could support this theory.^{10,34} Another explanation might be that the filtration of cystatin C, a positively charged 13,343- Da molecule might be different¹⁰ due to some physiological or abnormal renal process in pregnancy. In the present study there was a statistically significant difference in the mean values of serum cystatin C between the three study groups ($p < 0.04$) and the results were consistent with the previous studies.^{10,11,14,35}

Serum creatinine is widely used as an indicator for GFR. Our study revealed that there was a statistically significant difference in the mean values of serum creatinine (1mg/dl=88.4umol/L) between the three study groups ($p < 0.001$). There was a significant increase in serum creatinine in pre-eclamptic patients in comparison with healthy controls in our study and were consistent with the previous studies.^{10,11,14,35} We did not observe any significant increase in serum creatinine in those who developed PIH in comparison with healthy controls and the results were inconsistent with only one study.¹¹

Uric acid is a catabolic product of endogenous and dietary nucleic acids. It is freely filtered through the glomerular membrane and then almost completely reabsorbed in the proximal tubuli. It is also actively secreted in the distal tubuli. Increased uric acid level is a key clinical feature of preeclampsia. Higher levels correlate with significant maternal and fetal morbidity and mortality and is shown to be useful as a predictor for fetal outcome in preeclampsia.^{36,37} In the present study there was a statistically significant difference in the mean values of serum uric acid (1mg/dl= 59.48 μmol/L) between the three study groups (p<0.001). There was a significant increase in serum uric acid in pre-eclamptic patients in comparison with healthy controls in our study and were consistent with the previous studies.^{10,11,14,35} We did not observe any significant increase in serum uric acid in those who developed PIH in comparison with healthy controls and the results were inconsistent with only one study.¹¹

In Conclusion the data of the present investigation demonstrates that the three serum markers are increased in PE in comparison with healthy controls at the end of pregnancy. In PIH there was an increase in serum cystatin C but not serum creatinine and serum uric acid. ROC analysis showed that that serum creatinine had a superior diagnostic accuracy for preeclampsia compared to that of serum uric acid or serum cystatin C and that the diagnostic accuracy of serum uric acid was better than that of serum cystatin C. The diagnostic accuracy of these markers is not much helpful in PIH. Our study is limited by its sample size with limited number of patients in the study groups (PIH, PE).

Measurement of these markers with their associated GFR early in pregnancy would be helpful in identification of patients at high risk of developing PIH/PE and its complications.^{13,38,39} Which renal markers, individually or in combination, measured during early pregnancy will identify patients at high risk for developing PIH/PE needs to be investigated.

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Conflicts of interest: None declared

Ethical approval: The study has been approved by the Institute's ethical committee

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