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Original Research Article

The role of cystatin c in the prediction of outcome in hypertensive disorders of pregnancy

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ABSTRACT

Background: Hypertensive disorders of pregnancy greatly influence the maternal and foetal outcome in terms of morbidity and mortality. Complications include involvement of the kidney and progression of the disease which leads to deterioration of renal parameters and function. If left unattended, oliguria and renal shutdown are serious sequelae. Hence the importance of monitoring serum concentrations of cystatin C, creatinine and uric acid. The present study was designed to understand the variations of these markers in pregnant women in this part of India.
Methods: Serum levels were therefore determined in samples from 75 healthy women at term as well as in 38 samples of patients with Gestational hypertension and in 30 patients with pre-eclampsia (PE). The values were analysed after tabulation and results subjected to statistical analysis using SPSS software programme.
Results: The levels of all three components were significantly higher in pre-eclamptic patients when compared to healthy controls with the mean±SD being 1.86±0.82 vs. 1.08±0.33 for cystatin C, 0.93±0.18 vs. 0.62±0.07 for creatinine and 7.02±1.92 vs. 4.04±1.06 for uric acid respectively. In gestational hypertension, cystatin C was significantly higher, 1.42±1.1 unlike creatinine, 0.84±0.16 and uric acid, 5.26±1.40.
Conclusions: In view of significant increase in serum cystatin C, creatinine and uric acid in hypertensive disorders of pregnancy compared to those of healthy pregnant women, in our study, we conclude that these parameters are of significant value if used as markers to predict the onset of GH/PE. This can be established after further and larger clinical trials.

Keywords: Cystatin C, Creatinine, Gestational hypertension, Pre-eclampsia, Renal Markers, Uric acid

INTRODUCTION

Pre-eclampsia is a major etiological factor of perinatal morbidity and mortality. It is a multisystem dysfunction which manifests as hypertension, and proteinuria and seizures if it turns into eclampsia. The major physiological change resulting in this condition is generalized systemic vasoconstriction arising from circulatory disturbances secondary to a generalized endothelial dysfunction caused by inflammation.[1] 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.[2] Preeclampsia and eclampsia constitute 75% of all causes of acute kidney injury in pregnancy, while sepsis (11%) is followed by haemorrhage (7.2%). Perinatal mortality rate is significantly higher with GFR of 70ml/min.[2]Renal function i.e, glomerular filtration rate (GFR) is presently being monitored by serum creatinine concentration. Serum creatinine, though widely used is significantly influenced by body weight, physical activity and diet. After filtration by the glomerulus, it is reabsorbed and then secreted by tubules. The secretion increases with increase in serum creatinine. Initially thus serum creatinine does not rise and remains normal till about

50% of renal function is lost. Thus there is a "creatinine blind area" where a decline in GFR upto even a moderate degree does not show in serum creatinine levels.[3,4] So serum creatinine measurement has been challenged with various drawbacks and other means of monitoring GFR have been introduced. Serum cystatin is a protease inhibitor synthesized by all nucleated cells is filtered out exclusively by glomerular filtration and it has been considered as a better maker than creatinine for GFR. Concentration of serum cystatin C is not affected by gender, age, race, protein intake, and muscle mass, unlike serum creatinine. When GFR decreases, cystatin C level begins to rise proportionately.[5,6] Serum creatinine and uric acid are standard tests used to evaluate and monitor renal function in established pre-eclampsia. However the value of creatinine in analyzing GFR is limited by the effect of the patient's muscle mass, tubular secretion and reabsorption, dietary intake and analytical difficulties. In our study we have tried to find a correlation of serum creatinine, cystatin C and uric acid in normal and hypertensive disorders of pregnancy.

METHODS

The study was conducted in Post Graduate Department of Obstetrics and Gynecology, Sheri-Kashmir Institute of Medical Sciences, Kashmir. 75 normal, 38 gestational hypertensions and 30 pre-eclampsia patients who presented at 37 weeks of gestation were included into the study after taking written informed consent from each. These patients were thoroughly assessed clinically and details of their demography, medical history, physical examination, investigations and outcomes were recorded. Patients were diagnosed as Gestational Hyperetnsion and pre-eclampsia as per the teachings of international society for the study of hypertension in pregnancy (ISSHP). According to these guidelines, patient is labeled as GH if systolic blood pressure ≥140 mmHg and or a diastolic blood pressure ≥90 mmHg for the first time after mid pregnancy and pre-eclampsia if urinary albumin excretion was 1+ (30mg/dl) along with above mentioned readings of blood pressure. All the patients who were included in this study were previously free of any cardiovascular, endocrine or renal dysfunction. Specific exclusion criteria were patients who had hypo/hyperthyroidism, smoker, on steroid treatment.

Proper guidelines were followed for measuring the blood pressure. Two measurements were taken 4 hours apart with sphygmomanometer. Blood sample of all the patients were sent to laboratory for measurement of serum creatinine, uric acid and cystatin C levels were measured using the nephelometry technique. An early morning or random mid-stream urine sample was collected for estimation of proteins. Two readings of 1+ (30 mg/dl) was diagnostic of pre-eclampsia.

All the data was collected and subjected to statistical analysis using SPSS Software programme.

RESULTS

There were total of 143 cases included in this study out of which 75 were control, 38 in gestational hypertension while 30 in pre-eclamptic group. There was no statistically significant difference in the mean values of maternal age, parity status but we found a statistically significant difference ($p < 0.05$) in the systolic blood pressure, diastolic blood pressure and urinary proteins (Table 1).

The mean age of patients in control was 25 years while in GH and PE groups it was 22.4 and 24.6 respectively. Mean systolic and diastolic blood pressure in control, GH and PE was 110.6/74.2, 152.3/102 and 168.2/110.1 (in mm Hg) respectively. The difference in blood pressures in all these groups was highly significant. There were no urinary proteins in 68 (47.55%) in control group and 24 (16.78%) in PIH group. Traces of urinary proteins were found in 7 (4.89%) in control group and 14 (9.79%) patients in PIH group. 21 (14.68%), 8 (5.59%) and 1 (0.69%) patients were having +1, +2 and +3 urinary proteins in pre-eclampsia group respectively. The differences in urinary proteins were significant statistically among these groups.

Table 1: Patient characteristics.

Parameters	Healthy controls (n= 75)	PIH (n=38)	Pre-eclampsia (n=30)
	Mean	**Mean**	**Mean**
Age (years)	25.0	22.4	21.2
BMI	23.4	23.8	24.6
Systolic blood pressure (mmHg)	110.6	152.3	168.2
Diastolic blood pressure (mmHg)	74.2	102	110.1
Urine proteins			
Nil	68	24	0
Traces	7	14	0
1+	0	0	21
2+	0	0	8
3+	0	0	1

The values of all the three laboratory parameters were compared and found significantly higher in pre-eclamptic group (Tabl2). The values for serum cystatin in pre-eclamptic group was 1.86±0.82, 0.93±0.18 for creatinine and 7.02±1.92 for uric acid respectively. In control group results were 1.08±0.33 for cystatin C, 0.62±0.07 for creatinine and 4.04±1.06 for uric acid respectively. In PIH cystatin C was 1.42±1.1 unlike creatinine, 0.84±0.16 and uric acid, 5.26±1.40. The levels of all three components were significantly higher in pre-eclamptic patients when compared to healthy controls, while in PIH cystatin C was significantly higher unlike creatinine, and uric acid.

Table 2: Mean values of S-cystatin C, S-creatinine and S-uric acid in the study groups.

Parameters	Controls (n= 75)	GH (n=38)	PE (n=30)	P value
	Mean	Mean	Mean	
Serum cystatin C (mg/L)	1.08±0.33	1.42±1.10	1.86±0.82	0.001
Serum creatinine (mg/dl)	0.62±0.07	0.84±0.16	0.93±0.18	0.001
Serum uric acid (mg/dl)	4.04±1.06	5.26±1.40	7.02±1.92	0.001

*Statistically Significant (P < 0.05)

DISCUSSION

Kidney function is of major concern in pre-eclampsia, the most serious hypertensive disease in pregnancy defined as hypertension with significant proteinuria.[7] The impairment in renal function needs to be monitored closely to ensure a timely delivery before serious renal damage occurs. Various parameters like serum concentrations of cystatin C, creatinine and uric acid have been used to monitor renal functions in hypertensive disorders of pregnancy.

Several international studies have been done on serum cystatin C levels in normal pregnancy and pre-eclampsia.[8-14] In our study we have found statistically significant difference in the mean values of serum cystatin C between normal, pregnancy induced hypertension and pre-eclampsia patients ($p<0.04$). Similar findings have been shown by various studies done by Strevens H et al and others Strevens et al have concluded that serum cystatin C may be used as a marker, not only for impaired renal function, but also for the degree of glomerular endotheliosis and increase in glomerular volume in pregnancy thus may be of significant value in the monitoring of pregnancies complicated by pre-eclampsia.[15]

Serum creatinine has been routinely used for monitoring of renal functions. In this study, we have found a significant increase in serum creatinine in pre-eclamptic patients in comparison with healthy controls. Same results were found in other studies as well.[14,15] While comparing the results of serum creatinine in GH and healthy controls our results were consistent with those of Strevens et al study which showed no significant increase in serum creatinine in these two groups.

Kidneys play a vital role in the metabolism of uric acid and it is an important predictor to understand the outcome of pregnancy in terms of maternal and fetal morbidity and mortality.[16,17] We noticed similar results for serum creatinine and uric acid in all the three groups. There was significant difference in the mean values of serum uric acid in uric acid levels between normal controls and pre-eclamptic patients. This has also been shown by other studies.[18,19] While between normal controls and PIH increase was not significant as also concluded by Strevens et al in their study.

There is conflicting evidence regarding the efficacy of this test but recent data is showing favour for the use of cystatin C assay in the diagnostic armamentarium of renal decline in preeclampsia. Cost is a major deterrent, especially in the low resource setting and among patients with lower socioeconomic status.

CONCLUSION

In our study, we found a definite positive correlation between renal dysfunction and rising Cystatin C levels and it is recommended that this test be used in monitoring and assessing patients with preeclampsia to decide on optimum mode of management. Further larger trials are need of the hour and cost factor for the test needs to be addressed definitively to bring the benefit to the mother at risk.

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