

# Serum Cystatin C compared with conventional renal function tests: A study in patients with pre-eclampsia

Shalvi Sharma<sup>1</sup>, Rajiv Kumar Ranjan<sup>1</sup>, Mamta Gupta<sup>2</sup>, Anjana Singh<sup>1</sup>, Ruchika Gupta<sup>3</sup>, Leela Pant<sup>4</sup>, Sompal Singh<sup>4\*</sup>

<sup>1</sup>Department of Biochemistry, Hindu Rao Hospital, Delhi, India

<sup>2</sup>Department of Gynecology & Obstetrics, Hindu Rao Hospital, Delhi, India

<sup>3</sup>Department of Pathology, All India Institute of Medical Sciences, New Delhi, India

<sup>4</sup>Department of Pathology, Hindu Rao Hospital, Delhi, India

**Keywords:** Cystatin C, Pregnancy, Pre-eclampsia, Creatinine, Uric acid.

## Abstract

**Objective:** The aim of this study was to evaluate the value of serum cystatin C in assessment of renal function and compare with conventional renal function tests.

**Methods:** For this study, 30 females with pre-eclampsia (cases) and 30 healthy pregnant females (controls) were included from antenatal clinics. Venous blood samples were collected for estimation of cystatin C, creatinine, urea, uric acid, lipid profile, protein, albumin, blood sugar and glycosylated hemoglobin. Spot urine samples were taken for measurement of microalbumin and creatinine. Appropriate statistical tests were applied for significance of difference.

**Results:** Serum levels of cystatin C and uric acid were significantly higher in cases ( $P$  value  $<0.001$  and  $0.002$ , respectively) compared to controls. Urinary microalbumin-creatinine ratio also showed highly significant difference between cases and controls. However, renal function markers like urea and creatinine did not show any difference between the healthy pregnant females and pre-eclamptic patients.

**Conclusion:** Serum cystatin C appears to be a superior marker of renal function compared to creatinine in patients with pre-eclampsia and should be routinely included in the investigative work-up of these patients.

**\*Corresponding author:**

Dr. Sompal Singh, Specialist, Department of Pathology, Hindu Rao Hospital, Malka Ganj, Delhi - 110007 (India)  
Phone: +91-9810873046; E-mail: sompal151074@gmail.com

**Date of Submission:** July 26, 2014

**Date of Acceptance:** Aug 15, 2014

**Date of Publishing:** Sept 28, 2014

**How to cite this paper:**

Sharma S, Ranjan RK, Gupta M, Singh A, Gupta R, Pant L, Singh S. Serum Cystatin C compared with conventional renal function tests: A study in patients with pre-eclampsia. *Annals of Pathology and Laboratory Medicine*. 2014;1(2):A6-A9

## Introduction

Pre-eclampsia is a syndrome typified by presence of hypertension, proteinuria and systemic vasoconstriction in a pregnant female.<sup>[1]</sup> The etiopathogenesis of this syndrome is hypothesized to involve insufficient placental function with imbalance of cysteine proteases and their inhibitors, mainly cystatin C.<sup>[2]</sup> Earlier cross-sectional studies have shown that cystatin C is better than serum creatinine in estimating renal function, mainly due to less dependence on age, sex, race and muscle mass with absence of tubular secretion.<sup>[3,4]</sup> Cystatin C has been shown to be a reliable marker of glomerular filtration rate in presence of mild to moderate renal impairment.<sup>[4]</sup>

In pregnancy, serum levels of cystatin C is usually increased in the third trimester due to reduced excretion and increased synthesis.<sup>[5]</sup> This rise is further augmented in pre-eclampsia due to functional and structural changes in kidneys.<sup>[6]</sup> Earlier studies have demonstrated the correlation of serum cystatin C with glomerular endotheliosis and in turn, with severity of pre-eclampsia.<sup>[7]</sup> An extensive review of the available indexed English literature failed to yield any report from our country of analysis of cystatin C in pre-eclamptic patients.

Hence, the present study is the first such report of maternal serum levels of cystatin C in pre-eclamptic patients and comparison with conventional renal function tests from our country.

## Materials and Methods

A total of 60 patients from antenatal clinics (30 with pre-eclampsia and 30 healthy pregnant females as controls) were included in this study. The study has been approved by the institutional Ethics Committee. Informed consent was taken from all patients.

Venous blood was collected for estimation of cystatin C, creatinine, urea, uric acid, lipid profiles, protein, glycosylated hemoglobin and blood sugar. Spot urine sample were also collected for measurement of microalbuminuria and urinary creatinine.

Serum cystatin C was estimated using a two reagent immunoturbidimetry assays on a fully-automated biochemistry analyzer (XL-300, ERBA Diagnostics Mannheim GmBH, Germany). For calibration, cystatin C calibrator (EU-FLO cystatin C calibrator, Accurex Biomedical Pvt. Ltd., Mumbai) supplied with kit was used.

Lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, VLDL), serum creatinine, urea, uric acid and total protein were estimated using appropriate reagents in a fully automated biochemistry analyzer (XL-300, ERBA Diagnostics Mannheim GmBH, Germany). Glycosylated hemoglobin was measured using Nycocard HbA1c test with Nycocard Reader II (Axis-Shield, Dundee, Scotland) utilizing the boronate affinity assay. Urinary micro albumin was determined by immunoturbidometric method on the automated analyzer.

Appropriate statistical tests were applied to find the significance of difference of various parameters between controls and pre-eclampsia patients.

## Result

The mean age group of both controls and cases was similar. Serum cystatin C concentrations were significantly higher in pre-eclamptic patients ( $1.31 \pm 0.4$  mg/L) compared to the healthy pregnant females ( $0.96 \pm 0.2$  mg/L) with p value of  $<0.001$  (highly significant)

Urinary microalbumin-creatinine ratio also showed a statistically significant difference, being higher in pre-eclampsia patients ( $P=0.008$ ).

Similarly, serum uric acid was also significantly higher in pre-eclampsia patients than controls ( $P=0.002$ ). Other parameters that revealed statistically significant difference include urinary micro albumin ( $P=0.015$ ), urinary creatinine ( $P=0.012$ ) and serum protein ( $P=0.029$ ).

Parameters like serum urea, creatinine, lipid profile, HbA1C, blood sugar and serum albumin did not show any significant difference between pre-eclampsia patients and healthy pregnant females. The detailed results are tabulated in Table 1.

## Discussion

Pre-eclampsia, a syndrome characterized by hypertension, proteinuria and systemic vasoconstriction, is one of the leading causes of maternal and fetal morbidity.<sup>[1]</sup> Although the exact etiology of pre-eclampsia is clear, insufficient placental function is thought to play a pivotal role. Studies have shown that association of pre-eclampsia with deficiency in the trophoblast invasion of maternal spiral arteries, leading to poor perfusion of fetoplacental unit.<sup>[8]</sup>

**Table 1: Comparison of various biochemical parameters between healthy pregnant females (controls) and pre-eclamptic patients (cases)**

Parameter	Controls	Cases	P value
S. Cystatin C (mg/L)	0.96 ± 0.2	1.31 ± 0.4	<b>&lt;0.001</b>
B. Urea (mg/dl)	18.93 ± 3.19	20.13 ± 4.91	0.584
S. Creatinine (mg/dl)	0.7 ± 0.08	0.71 ± 0.09	0.907
S. Cholesterol (mg/dl)	228.07 ± 31.8	239.53 ± 51.8	0.228
S. HDL Cholesterol (mg/dl)	63.5 ± 5.6	63.63 ± 22.1	0.2
S. LDL Cholesterol (mg/dl)	135.37 ± 40	129.03 ± 40.9	0.842
S. HbA1c (%)	4.98 ± 0.4	5.02 ± 0.5	0.807
B. Glucose (g/dl)	87.63 ± 21.3	88.0 ± 22.5	0.994
S. Protein (g/dl)	6.0 ± 0.4	5.71 ± 0.4	<b>0.029</b>
S. Albumin (g/dl)	3.28 ± 0.2	3.46 ± 1.8	0.09
S. Uric acid (mg/dl)	4.58 ± 1.2	5.92 ± 1.5	<b>0.002</b>
Urine microalbumin (mg/dl)	31.76 ± 9.2	38.53 ± 12.7	<b>0.015</b>
Urine creatinine (mg/dl)	17.91 ± 12.9	10.3 ± 8.0	<b>0.012</b>
Urine microalbumin-creatinine ratio	4.27 ± 2.4	6.32 ± 3.9	<b>0.008</b>

Trophoblast invasion is a complex process, which involves concerted action of adhesion, degradation and migration process and requires a balance of degradation enzymes and their inhibitors.<sup>[1]</sup> Cathepsins (cysteine-proteases) are considered to be important for trophoblast invasion while their inhibitor, cystatin C, regulates this invasion to prevent formation of placenta accreta or percreta.<sup>[2]</sup>

Cystatin C is a low molecular weight (13.3KDa) protein having renal excretion. Serum levels of cystatin C are less dependent on age, sex, race and muscle mass compared to serum creatinine levels.<sup>[3]</sup> Cross-sectional studies have shown that serum levels of cystatin C are more precise in estimating kidney functions than serum creatinine. This may be because creatinine is actively secreted by proximal renal tubules and hence glomerular filtration rate, calculated by creatinine clearance, is overestimated in severe renal dysfunction.<sup>[4,9]</sup> Newman et al in their study concluded that cystatin C was more sensitive marker for small changes in GFR.<sup>[10]</sup> In a systematic review, Roos et al reported that cystatin C was a reliable marker of GFR in patients with mild to moderate renal function impairment and also had a higher chance of detecting true renal impairment.<sup>[4]</sup>

Serum levels of cystatin C are increased in normal pregnancy, especially in the third trimester. This has been attributed to attend renal handling of low molecular weight proteins in conjunction with a decreased GFR and increased synthesis by the foeto-placental unit or generalized phenomenon.<sup>[5,6]</sup>

The levels of Cystatin C are further increased in pre-eclampsia, correlating with the functional and structural changes in kidneys.<sup>[6]</sup> A study by Strevens et al. demonstrated that maternal serum levels of Cystatin C was a good marker for most onsets and severity of pre-eclampsia.<sup>[5]</sup> In a renal biopsy study Cystatin C levels were shown to correlate with the degree of glomerular endotheliosis, a typical histologic feature of pre-eclampsia.<sup>[7]</sup> Since degree of endotheliosis has been considered to determine the severity of pre-eclampsia, it has been hypothesized that serum levels of Cystatin C can offer information regarding the severity of pre-eclampsia.<sup>[7,11]</sup>

In the present study also, serum Cystatin C levels were significantly higher in patients with pre-eclampsia than healthy pregnant females. On the other hand, serum creatinine levels did not show significant difference between the two groups. These results confirm the previous observation of Cystatin C being superior to serum creatinine for estimation of renal function in pre-eclampsia patients.

Urinary creatinine, rather than serum creatinine, showed significant difference between controls and pre-eclampsia patients. Similar was the case with urinary microalbumin with resultant significant difference in the urine microalbumin-creatinine ratio between healthy pregnant females and pre-eclampsia patients. These results are in consonance with those of previous authors.<sup>[12]</sup>

Hyperuricemia is also a frequent finding in pre-eclamptic pregnancies and has been considered

to result from altered renal function. However, few earlier studies have shown an increased risk of fetal death in pre-eclampsia with elevated uric acid.<sup>[13]</sup> A case control study showed that elevated serum uric acid in setting of chronic hypertension could identify females with increased likelihood of developing superimposed pre-eclampsia.<sup>[14]</sup> In the present study also, serum uric acid was significantly higher in patients with pre-eclampsia compared with controls.

## Conclusion

In conclusion, the present study reiterates that serum Cystatin C levels appear to be better indicator of altered renal function in pre-eclamptic patients than serum creatinine and should be included in the investigative workup of these patients.

## Acknowledgements

None.

## Funding

None.

## Competing Interests

None declared

## References

1. Redman CW, Sargent IL. Latest advances in understanding pre-eclampsia. *Science* 2005; 308:1592-4.
2. Ishida M, Ono K, Taguchi S, Ohashi S, Naito J, Horiguchi K, et al. Cathepsin gene expression in mouse placenta during the latter half of pregnancy. *J Reprod Dev* 2004;50:515-23.
3. Shlipak MG. Cystatin C as a marker of glomerular filtration rate in chronic kidney disease: influence of body composition. *Nat Clin Pract Nephrol* 2007;3:188-9.
4. Roos JF, Doust J, Tett SE, Kirkpatrick CM. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children: a meta analysis. *Clin Biochem* 2007;40:383-91.
5. Strevens H, Wide-Swensson D, Grubb A. Serum cystatin C is a better marker for pre-eclampsia than serum creatinine or serum urate. *Scand J Clin Lab Invest* 2001;61:575-80.
6. Strevens H, Wide-Swensson D, Torffvit O, Grubb A. Serum cystatin C for assessment of glomerular filtration rate in pregnant and non-pregnant women: indications of altered filtration process in pregnancy. *Scand J Clin Lab Invest* 2002;62:141-7.
7. Strevens H, Wide-Swensson D, Grubb A, Hansen A, Horn T, Ingemarsson I, et al. Serum cystatin C reflects glomerular endotheliosis in normal, hypertensive and pre-pregnancies. *BJOG* 2003;110:825-30.
8. van den Brûle F, Berndt S, Simon N, Coulon C, Le Goarant J, Munaut C, et al. Trophoblast invasion and placentation: molecular mechanisms and regulation. *Chem Immunol Allergy* 2005; 88:163-80.
9. Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitation of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int* 1985;28: 830-8.
10. Newman DJ, Thakkar H, Edwards RG, Wilkie M, White T, Grubb AO, et al. Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. *Kidney Int* 1995;47:312-8.
11. Spargo B, McCartney CP, Winemiller R. Glomerular capillary endotheliosis in toxemia of pregnancy. *Arch Pathol* 1959;68:593-9.
12. Salako BL, Olayemi O, Odukogbe AT, Adedapo KS, Aimakhu CO, Alu FE, et al. Microalbuminuria in pregnancy as a predictor of pre-eclampsia and eclampsia. *West Afr J Med* 2003;22:295-300.
13. Redman CW, Beilin LJ, Bonnar J, Wilkinson RH. Plasma urate measurements in predicting fetal death in hypertensive pregnancy. *Lancet* 1976;1:1370-3.
14. Lim KH, Friedman SA, Ecker JL, Kao L, Kirkpatrick SJ. The clinical utility of serum uric acid measurements in hypertensive diseases of pregnancy. *Am J Obstet Gynecol* 1998; 178:1067-71.



This work is licensed under the Creative Commons Attribution International License (CC BY).