**Original article:**

# Study of comparative estimation of serum  Cystatin C and serum creatinine in pre-eclamptic patients and normal pregnant woman

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**Abstract:**

**Introduction:** Preeclampsia a multisystem and multifactorial disease. Manifestations begin early in pregnancy which affects late gestation. Consequences of Preeclampsia are mostly due to endothelial dysfunction, vasospasm and ischemia [4]. Creatinine is most widely used biomarker of GFR.

**Methodology:** This Hospital based cross sectional study entitled  ―Serum Cystatin C levels as alternative marker of renal function in pre-eclampsia"is a cross sectional study and was conducted in Department of Biochemistry with the help of Obstetrics and Gynaecology Department during period Nov 2016 to December 2017 .

**Results:** Our study results have shown that serum Cystatin C levels in Preeclamptic group were significantly higher ($1.62\pm0.325$) than that of non Preeclamptic group ($0.88\pm0.205$mg/L,

P <0.0001) (table no 18). Also 80% of Preeclamptic patients were showing Cystatin C levels higher than control group's reference range, while 22.8% of Preeclamptic patients were showing Creatinine levels higher than control group's reference range.

**Conclusion:**  In our study, 22.8% of Preeclamptic patients were having high Creatinine levels, while 80% of patients were showing high Cystatin C levels as compared to control group's reference range.

**Keywords :** Serum Cystatin C , Preeclampsia , serum creatinine level

## Introduction:

Worldwide incidence of Preeclampsia is 4-8%[18] 60,000 women die each year from pre- eclampsia world-wide [1]Pre-eclampsia has remained a significant public health threat in  both developed and developing countries contributing to maternal and perinatal morbidity and mortality globally[2].In India the incidence of Preeclampsia is reported to be 8-10% According to a study in India, Prevalence of Preeclampsia in India is 5.4%. Overall 10%-15% of maternal deaths are directly associated with Preeclampsia [2].

Also Preeclampsia is 2nd leading cause of fetal deaths [3]. 500,000 infant deaths each year worldwide are caused by Preeclampsia [2].Approximately 12 to 25% of fetal growth restriction and small for gestational age infants occurs due to Preeclampsia. Overall 15 to 20% of all preterm births are attributable to Preeclampsia. Complications of prematurity are ultimately leads to neonatal deaths and serious long-term neonatal morbidity [4].

Preeclampsia a multisystem and multifactorial disease. Manifestations begin early in pregnancy which affects late gestation. Consequences of Preeclampsia are mostly due to endothelial dysfunction, vasospasm and ischemia [4]. Creatinine is most widely used biomarker of GFR. Use Of creatinine as biomarker was firstly introduced by Rohberg in 1926; exogenously administered creatinine was used by him. In 1937 Popper and Mandel developed the use of endogenous creatinine clearance. Creatinine is an amino acid derivative required to restore adenosine triphosphate (ATP) via the Creatine kinase reaction. Creatinine is a cation having low Molecular mass of 113 Da [5].

Cystatin C has been shown to provide superior diagnostic accuracy for pre-eclampsia compared to serum urate and creatinine, and not only be used as a marker for impaired renal function, but also for the degree of glomerular endotheliosis the only consistently found as pathological lesion in Preeclampsia[6]. With this view , present study was planned to estimate the serum levels of Cystatin C and serum creatinine in pre-eclamptic patients and normal pregnant woman.

**Methodology:**

This Hospital based cross sectional study entitled  ―Serum Cystatin C levels as alternative marker of renal function in pre-eclampsia"is a cross sectional study and was conducted in Department of Biochemistry with the help of Obstetrics and Gynaecology Department during period Nov 2016 to December 2017 .All the study subjects were examined and investigated according to predesigned proforma. The study was approved by institutional Ethics Committee for research work Informed written consent was obtained from all the study subjects enrolled in the study.

Sample size Estimation: (104) Sample size was calculated from Open Epi software with 95%CI Sample Size=4PQ/L2 , P=prevalence, Q= (100-P), L=Error percentage

The prevalence of Preeclampsia is 5.4% (20) while the error percentage is taken as 8%.

**Results:**

The study population consist of 70 pregnant women of whom, 35 were normotensive healthy pregnant women as controls and 35 pregnant women diagnosed with Preeclampsia. All subjects of study population selected for present study were attending and admitted to tertiary health centre, who were all Primigravida aged between 20 to 35 years having gestational age >20 and <35 weeks.

**Inclusion criteria**

Cases-:

- Preeclamptic Primigravida having gestational age >20 weeks and <35 weeks of pregnancy
- Age – 20 to 35 years
- BP – greater than or equal to140/90 mm Hg (ACOG criteria)
- Urine albumin ≥ 1 + dipstick or 300 mg per 24 hour urine

Controls-:

- Normal Primigravida pregnant women in having gestational age >20 weeks and<35 weeks of pregnancy
- Age – 20 to 35 years
- BP – Normotensive having Blood Pressure <140/90
- Urine albumin < 1 + dipstick or 300 mg per 24 hour urine

Exclusion criteria

- Age < 20 years and > 35years

- Gestational age<20 weeks or >35 weeks

- Multigravida with more than one Para

- Previous history of hypertension

- Previous history of diabetes mellitus

- Previous history of thyroid disorder

- Previous history of dyslipidemia

- Family history of Preeclampsia

- Previous history of renal disease

- Patients with history of convulsions

After explaining all details, informed consent was taken from each subject for participation in this study. History of patient was recorded on preformed questionnaire which included detailed history about present pregnancy, family history of Preeclampsia and exclusion criteria. The subjects and controls were examined for vital signs like pulse and blood pressure Blood pressure was measured in sitting as well as supine position, first by palpatory method and then by auscultatory method.

**Results:**

Mean age for Preeclampsia group was found to be 27.4 years while in controls it was found to be 25.6 years (Mean ±SD of cases=27.40±4.195 years and that of controls= 25.66±3.857 years) .these values suggest that mean age of distribution among two groups is not significantly different . The mean gestational age in Preeclamptic group was found to be 27.78 weeks and in controls was found to be 26.97 weeks (Mean ±SD of cases=27.78±3.568 weeks and that of controls= 26.97±4.305 weeks).these values suggest that mean gestational age distribution among two groups is not significantly different.

<u>**Table**</u>**1-  Comparison of Creatinine-P value**

| Group | Number | Mean | Std. Deviation | Unpaired t | P |
|---|---|---|---|---|---|
| Preeclampsia group | 35 | 0.80 | 0.167 | 4.536 | <0.0001 HS |
| Controls | 35 | 0.64 | 0.131 | | |

The Mean creatinine levels in Preeclamptic group isn0.8 mg/dl and control group is0.64 mg/dl.(Mean ±SD of cases=0.8±0.167 and that of controls = 0.64±0.131).These values suggests there is highly significant difference in creatinine levels in between 2 groups.

**Table 2  Comparison of Cystatin C-P value**

| Cystatin C | Number | Mean | Std Deviation | Unpaired t | P |
|---|---|---|---|---|---|
| Preeclampsia | 35 | 1.62 | 0.325 | 11.412 | <0.0001 |
| Controls | 35 | 0.88 | 0.205 | | HS |

The Mean Cystatin C levels in Preeclamptic group is 1.62mg/L and control group is0.88 mg/l Mean ±SD of Preeclamptic group=1.62±0.325 and that of controls= 0.88±0.205mg/L )these values suggests there is highly significant difference in Cystatin C levels in between 2 groups.

In Preeclampsia group, Cystatin C levels are found to be higher also it is correlated with creatinine levels. (r=0.467,P=0.005).

In our study reference Range of Cystatin C and creatinine in normal pregnancy control group is 0.62-1.4 mg/L and 0.4-0.9 mg/dl respectively.

Among Preeclampsia group only 22.8% patients have creatinine levels more than reference range of controls while 80% of patients has higher Cystatin C levels than reference range of controls.

For Cystatin C cutoff value of 1.11mg/dl had sensitivity of 91.4% and a specificity of 85.7% for serum creatinine concentration higher than 0.65mg/dl had a sensitivity of 82.9% and a specificity of 57.9%.

**Receiver Operating Characteristic Curve (ROC curve)analysis for Creatinine and Cystatin C:**
ROC analysis was done which showed that serum Cystatin C (AUC 0.967)more accurate when compared to serum creatinine (AUC 0.768) taking Cystatin C cutoff as 1.11mg/L and creatinine cutoff as 0.65mg/dl.

**Table 3 Area under curve (AUC) And Confidence Interval (CI)**

| | AUC | 95% CI | |
|---|---|---|---|
| Creatinine | 0.768 | 0.658 | 0.877 |
| Cystatin C | 0.967 | 0.933 | 1.000 |

Cystatin C is considered an endogenous marker of kidney function [76]. As Preeclampsia involves renal system it can cause elevation of Cystatin C in serum of Preeclamptic patients. Studies have been carried out to assess importance of Cystatin C as severity indicator as well as progress of preeclampsia

Cystatin C is freely filtered and almost completely reabsorbed in kidney. So, Cystatin C could be an excellent indicator of GFR [61].

Considering these facts evaluation of creatinine and Cystatin C was done in diagnosed patients of preeclampsia as well as in normal pregnant women as controls.

**Discussion:**

Evaluation of CRP and ESR was also done to rule out rise of Cystatin C as a part of acute inflammation. The present study was carried out on 70 subjects The patients were divided into two groups; 35 diagnosed cases of preeclampsia (Group 1) and 35 normal pregnant women were studied as controls (Group 2) Diagnosis of Preeclampsia was based on presence of proteinuria and BP greater than or equal to140/90 and presence of proteinuria [7].Results were compared among the 2 Groups. The study protocol was approved by the Ethical Committee of the Institute Informed written consent was obtained from all the study subjects enrolled in the study.

Age group of patients in present study is between 20 to 35 years. Mean age in Preeclamptic group is found to be 27.4 years and 25.6 years in control group. Mean age in Preeclamptic group is slightly higher as compared to normotensive pregnant women group. (table no11) Mean Gestational age of Preeclamptic group found to be 27.78 weeks and 26.97 weeks in normotensive pregnant women control group. We found mean gestational age was higher in preeclampsia group.

Serum Cystatin C is a reliable marker of GFR in pregnant women when levels were compared to healthy nonpregnant women. In PE, the serum concentration of Cystatin C relates significantly to structural and functional changes in the kidneys [6].

Cystatin C does not cross the placental barrier, and previous studies have found no  correlation between maternal and neonatal serum .Cystatin C values suggesting that neonatal serum Cystatin C originates almost exclusively in the neonate thus having no effect on the maternal Cystatin C levels [8].

Our study results have shown that serum Cystatin C levels in Preeclamptic group were significantly higher (1.62±0.325) than that of non Preeclamptic group (0.88±0.205mg/L,

P <0.0001) (table no 18). Also 80% of Preeclamptic patients were showing Cystatin C levels higher than control group's reference range, while 22.8% of Preeclamptic patients were showing Creatinine levels higher than control group's reference range. Similar results were obtained by Strevens et al[9] Sherif Saleh et al[10] , Hong-Xia Guo[11]Huang QT et al[12],However Yalamati et al observed that Cystatin C levels were not associated with maternal and fetal outcome studied in Hypertensive pregnancies[13].

**Conclusion:**

In our study, 22.8% of Preeclamptic patients were having high Creatinine levels, while 80% of patients were showing high Cystatin C levels as compared to control group's reference range.

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