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RESEARCH ARTICLE

STUDYOF SERUM CYSTATIN C IN PRE-ECLAMPSIA

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ABSTRACT

Background: Pre-eclampsia is a common complication of pregnancy constituting major cause of maternal and foetal morbidity and mortality. It develops in 4% - 5% of pregnancies. Altered renal function is an essential component of the patho-physiology of pre-eclampsia, which could lead to acute renal failure. The kidneys play a significant role in the turnover of low molecular weight substances like Urea, Creatinine, Uric acid and Cystatin C.

Aims and Objectives: To study serum cystatin C in pre-eclampsia and compare it with serusm Creatinine. To assess whether serum cystatin C is an early and better marker than Creatinine of renal dysfunction in pre-eclampsia.

Materials and Methods: A Case - control study comparing 30 pre-eclampticprimigravida inthe third trimester with 30 normotensive primigravida of same gestational age from Vani Vilas Hospital, Bangalore. No history of Hypertension, Diabetes mellitus or Renal disease in cases and controls.

Results: Serum Cystatin C was found to be increased in pre-eclamptic patients when compared to controls. Serum Creatinine was within reference range in both cases and controls.

Conclusion: Serum Cystatin C is an early and better marker of renal dysfunction in pre-eclampsia compared to serum Creatinine**.**

INTRODUCTION

Pre-eclampsia is a multisystem disorder of unknown etiology characterized by development of hypertension to the extent of 140/90 mmHg or more with proteinuria after 20 weeks of pregnancy in a previously normotensive and non-proteinuric patients (Dutta ?). Pre-eclampsia stands out among the hypertensive disorders for its impact on maternal and neonatal health. It is one of the leading causes of maternal and perinatal mortality and morbidity worldwide. The incidence of pre-eclampsia has continued to increase worldwide, and it is associated with significant maternal morbidity and mortality, accounting for about 50,000 deaths worldwide annually. The incidence of pre-eclampsia in primigravidae is about 4 - 5% (WHO 2011 and Duley 2009). Reducing maternal mortality by 75% between 1990 and 2015 has been considered as part of the millennium development goals of the World Health Organization (WHO) Nations (WHO, 2011) There is extensive evidence that the reduction of uteroplacental blood flow in this syndrome results from the toxic combination of hypoxia, imbalance of angiogenic and antiangiogenic factors, inflammation, deranged immunity and oxidative stress. (EloshaEiland *et al.,* 2012). Altered renal function is an essential component of the patho-physiology of pre-eclampsia, which could lead to acute renal failure - an important cause for maternal morbidity and mortality (Elisabeth coll 2000). Women treated for preeclampsia also have an increased risk for cardiovascular and renal disease (Vikse *et al.,* 2008). The majority of deaths due to pre-eclampsia and eclampsia are avoidable through the provision of timely and effective care to the women presenting with these complications. (WHO, 2011) Cystatin C is a low molecular weight non glycosylated basic protein of 12.8kDa made of 120 amino acid residues expressed in all nucleated cells. Cystatin C is produced at constant rate and is freely filtered by kidney glomeruli, completely reabsorbed but degraded in the tubules thus making it an excellent GFR marker. It is most abundant extra cellular cysteine protease inhibitor. The blood levels are not dependent on age, sex, diet, muscle mass or inflammatory processes. With regard to renal function, its most important attributes are its small size and high isoelectric point (PI=9.2) which enable it to be more freely filtered. It is sensitive to changes in the Creatinine blind area of GFR (40-70ml/min/1.73 m^2). Since there is no tubular secretion of Cystatin C, it is extremely sensitive to minor changes in GFR in the earliest stages of kidney diseases. The gene has been sequenced and the promoter region has been identified as of the housekeeping type, with no regulatory elements. The Cystatin C gene is called CST3. There are no known extra renal routes of elimination, with clearance from the circulation is only by glomerular filtration. Cystain C can be measured by particle enhanced nephlometricimmunoassay. Cystatin C measurement is unaffected by the spectral interferences affecting Creatinine assays. (Vasudevan *et al.,* ? and Carl A Burtis *et al.,* 2006) Creatinine is the most widely used biomarker of kidney function and is insensitive in the early stages of renal

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impairment. (Elosha Eiland *et al.,* 2012) Creatinine is 113 da is an anhydride form of Creatine that is produced as the final product of decomposition of phospho-creatine. It is present in all body fluids and secretions and is freely filtered by the glomerulus and not reabsorbed by the renal tubules to a great extent. Creatinine has no useful function and is eliminated by renal glomerular filtration and to a small extent by renal tubular secretion. Most of the body creatine is found in muscle tissue where it is present as Creatine phosphate and serves as a highenergy storage reservoir for conversion to adenosine triphosphate. Creatine is synthesized in liver, kidneys and pancreas by two enzymatically mediated reactions. Creatine is then transported in blood to other organs, such as muscle and brain. The amount of Creatinine productions each day is constant and is related to muscling mass. Excretion of Creatinine depends on skeletal muscle mass and varies with age, sex and diet. Creatinine assays are conducted for diagnostic purposes, for therapeutic monitoring of acute and chronic renal diseases and for monitoring patients on renal dialysis. Serum Creatinine levels are elevated in patients with renal malfunction especially with the significant decrease in glomerular filtration. A normal serum creatinine level does not rule out the presence of impaired renal function. Creatinine is unable to detect reduced GFR in early stages of kidney dysfunction hence search for new biomarker like Cystatin C. (Carl A Burtis *et al.,* 2006 and Bhagavan *et al.,* 2011)

Objectives

- To estimate serum cystatin C and serum Creatinine level in pre-eclamptic primigravidae and compare it with controls.
- To assess the diagnostic performance of serum Cystatin C in early detection of renal dysfunction in pre-eclamptic primigravidae by comparing it with serum Creatinine.

METHODOLOGY

- Study Design: CaseControl Study
- Cases - 30 pre-eclamptic primigravidae in third trimester of pregnancy
- Controls - 30 healthy primigravidae in third trimester
- Inpatients and outpatients of Vani Vilas Hospital, BMC&RI, Bangalore
- Estimation of serum Creatinine by Jaffe's method.
- Estimation of Cystatin C by Nephelometric method

Inclusion criteria

- Pre-eclamptic primigravidae in third trimester-cases
- Healthy primigravidae in third trimester-controls

Exclusion criteria

- Pre-eclamptic multigravidae
- Healthy multigravidae
- Known case of diabetes mellitus, renal disease and hypertension

RESULTS and DISCUSSION

Comparison between cases and controls

	MEAN	SD
CREATININE		
Cases	.61	.17
Controls	.47	.08
CYSTATIN C		
Cases	1.29	.4
Controls	.77	.13

Creatinine

P value	<.0001
t value	4.0813
Df	58

Cystatin C

P value	.0001
t value	6.77
Df	58

Cystatin C in cases

Sensitivity	76.7%
Specificity	86.7%
Positive predictive value	85.2%

In this study, means Cystatin C levels in cases was 1.29 with SD 0.4 and in controls mean Cystatin C level was 0.77 and SD 0.13. This study showed mean serum Cystatin C level had elevated significantly in cases when compared to controls. In this study mean Creatinine level in cases 0.61 with SD 0.17 and in controls the mean Creatinine level 0.47 and SD 0.08. There was no significant elevation of serum Creatinine either in cases or controls. At given cut off, Creatinine was not positive for either cases or controls, whereas Cystatin C was positive for around 77% of cases. Based on sensitivity, specificity and positive predictive value, the Cystatin C in cases showed to be a better screening test for early detection of renal dysfunction among pre-eclamptic cases when compared to Creatinine. Unpaired t - test was conducted to evaluate significance of difference of mean values of Creatinine and Cystatin C between cases and controls. Both the differences were statistically significant among cases and controls. Estimation of serum Cystatin C in this study showed significant elevation in cases when compared to controls. Correlation between serum Cystatin C and serum Creatinine showed that serum Cystatin C had elevated in cases when compared to serum Creatinine which was within reference range. This is in accordance with several studies on serum Cystatin C, Creatinine, and Uric acid in pre-eclampsia, Which shows that Serum Cystatin-C seems to reflect the GFR precisely in women with severe preeclampsia and can be a good marker to monitor the renal function from antepartum to postpartum. (Guo Hx *et al.,* 2012; Stevens *et al.,* 2001; Kristensen *et al.,* 2007; Stevens *et al.,* 2002; Aleksandra Nikolic *et al.,* 2011) Cystatin C is superior to Creatinine in early detection of renal dysfunction; it increases when renal impairment is low or minimal and detects renal impairment earlier than Creatinine. Several studies conducted on cases other than pre-eclampsia like cirrhosis, And diabetics showed that serum Cystatin C is the useful marker in detecting renal dysfunction and better marker than creatinine. (Purnima Dey Sarkar *et al.,* 2005; Stefan Herget-Rosenthal *et al.,* 2004; Michele Mussap *et al.,*2002; Gerbes *et al.,* 2002)

Conclusion

- There was significant elevation of serum Cystatin C above the reference range in cases when compared to serum Creatinine, which did not rise.

- Hence serum Cystatin C has a superior diagnostic utility for renal impairment in pre-eclampsia compared to serum Creatinine - the current standard marker

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