ORIGINAL RESEARCH PAPER

Obstetrics & Gynaecology

A STUDY OF MATERNAL SERUM CYSTATIN C AND SERUM CREATININE LEVELS IN PREECLAMPTIC AND NORMOTENSIVE PREGNANCIES-A CASE CONTROL STUDY

KEY WORDS: Pre Eclampsia, Serum cystatin C and Serum Creatinine.

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ABSTRACT

Background: Preeclampsia is a multisystem disorder that is specific to human pregnancy. It is characterized by the development of hypertension to the extent of 140/90 mm Hg or more on atleast two occasions 4 hours apart with proteinuria more than 300mg for 24hrs or urine proteinuria more than 1+ that occurs after 20 weeks of gestation in a previously normotensive and nonproteinuric woman [17].

BENEFITS OF THE STUDY The better marker of renal dysfunction in preeclampsia can be used in clinical settings –serum cystatin C / serum creatinine.

Materials & Methods: Term primi gravidae attending AN OPD who are diagnosed to have preeclampsia are included and compared to equal number of healthy matched normo tensive pregnant women

Cases - pre-eclamptic primi gravidae in third trimester of pregnancy.

Controls – healthy primi gravidae in third trimester.

STUDY DESIGN:- Case control study

PLACE OF STUDY: Antenatal Outpatient Department, LABOR WARD AND ANTENATAL WARD Dept of Obstetrics & Gynaecology, Govt Kilpauk medical college & Hospital, Chennai.

Results The mean age group, gestational age and parity of both controls and cases was similar. Serum cystatin C concentrations were significantly higher in pre-eclamptic patients (0.895 ±0.310mg/L) compared to the healthy pregnant females (0.489 ± 0.064 mg/L) with p value of <0.001 (highly significant). Serum levels of cystatin C are increased in normal pregnancy, especially in the third trimester.

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

Introduction:

Preeclampsia is a multisystem disorder that is specific to human pregnancy. It is characterized by the development of hypertension to the extent of 140/90 mm Hg or more on atleast two occasions 4 hours apart with proteinuria more than 300mg for 24hrs or urine proteinuria more than 1+ that occurs after 20 weeks of gestation in a previously normotensive and nonproteinuric woman [17]. It is associated with high maternal mortality and morbidity and increased risk of perinatal death, preterm birth, and intrauterine growth restriction. It has been reported to complicate 4–7% of pregnancies worldwide.

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.

CYSTATIN C

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 [20]. It is a potent inhibitor of lysosomal proteinases and probably one of the most important extracellular inhibitors of cysteine proteases. Cystatin C belongs to the type 2 cystatin gene family.

It is extremely sensitive to minor changes in GFR in the earliest changes of kidney disease.

CREATININE

Creatinine is a breakdown product of creatinine phosphate in muscle, and is usually produced at a constant rate by the body. Serum creatinine is an important indicator of renal health because it is an easily measured byproduct of muscle metabolism that is excreted unchanged by the kidneys[9].

Creatinine is removed from the blood chiefly by the kidneys primarily by glomerular filtration but also by proximal tubular secretion. Little or no tubular reabsorption of creatinine occurs. If the filtration in the kidney is deficient, creatinine blood levels rise. Therefore, creatinine levels in blood and urine may be used to calculate the creatinine clearance (CrCl), which correlates with the glomerular filtration rate (GFR). Blood creatinine levels may also be used alone to calculate the estimated GFR (eGFR)[11].

Diagnosis of Hypertension:

Hypertension in pregnancy should be defined as:Systolic blood pressure greater than or equal to 140 mmHg. Diastolic blood pressure of greater than or equal to 90 mmHg.These measurements should be based on the average of at least two measurements, taken using the same arm, 4-6 hours apart. Elevations of both systolic and diastolic blood pressures have been associated with adverse fetal outcome and therefore both are important. Detecting a rise in blood pressure from booking or preconception blood pressure, rather than relying on an absolute value, has in the past been considered useful in diagnosing preeclampsia in women who do not reach blood pressure of 140 or 90 mmHg. Available evidence does not suggest that these women have an increased risk of adverse outcome. However, such a rise may be significant in women with other complications such as proteinuria and closer monitoring of such women is recommended. Severe hypertension should be defined as a systolic BP of >160 mmHg or a diastolic BP of >110 mmHg.

AIMS & 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.

BENEFITS OF THE STUDY

The better marker of renal dysfunction in preeclampsia can be used in clinical settings –serum cystatin C / serum creatinine

METHODOLOGY

1) Term primigravidae attending AN OPD who are diagnosed to have preeclampsia are included and compared to equal number of healthy matched normotensive pregnant women
2) Detailed history, general examination, obstetric examination are performed
3) Withdrawal of 5ml blood for serum cystatin C& serum creatinine estimation

Cases - pre-eclampticprimigravidae in third trimester ofpregnancy
Controls - healthyprimigravidae in third trimester

Inpatients and outpatients of O & G Department, GovtKilpauk medical college & Hospital, Chennai

Estimation of serum Creatinine by Jaffe's method.

Estimation of Cystatin C by Nephelometric method

STUDY DESIGN:- Case control study

PLACE OF STUDY:

Antenatal Outpatient Department, LABOR WARD AND ANTENATAL WARD Dept of Obstetrics & Gynaecology, Govt Kilpauk medical college & Hospital, Chennai

DURATION OF STUDY: 6 Months

SAMPLE SIZE

cases – 40
control - 40

INCLUSION CRITERIA:-

- Pre-eclamptic primigravidaein third trimester as cases
- Healthy matched primigravidae in third trimester as controls

EXCLUSION CRITERIA:

Pre-eclamptic multigravidae Healthy multigravidae

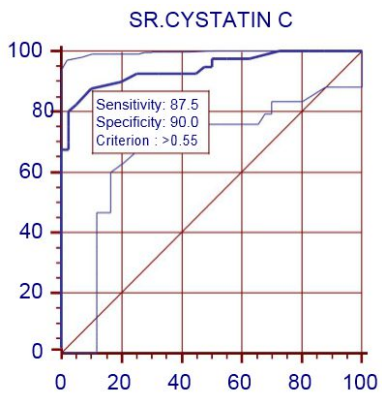
RESULTS

TABLE 1: COMPARISON OF MEAN SERUM CYSTATIN C

Pre-eclampsia	Serumcystatin C Mean±STD	Mean difference	95% CI Lower	95% CI Upper	P value
YES	0.895 ± 0.310	0.41	0.30	0.50	<0.001
NO	0.489 ± 0.064				

The mean of serum cystatin C among people with preeclampsia was 0.895 ± 0.310 and the mean serum cystatin C among people without preeclampsia was 0.489 ± 0.064 in the study population. Hence Serum Cystatin C was 0.41 units higher (95% CI 0.30 to 0.50, p value <0.00) in people with preeclampsia (Table 1)

DIAGRAM :1



Area under the ROC curve (AUC)

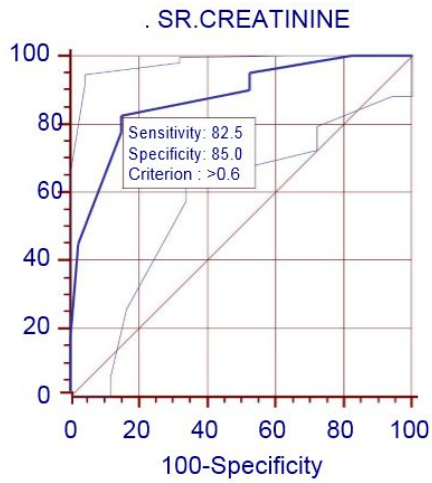
Area under the ROC curve (AUC)	0.941875
Standard Error[a]	0.0259
95% Confidence interval[b]	0.865947 to 0.981859
z statistic	17.031
Significance level P (Area=0.5)	<0.0001

From Diagram 1, we derive that serum crystatin C has got 87.5% sensitivity and Specificity 90%, Area under curve is 0.941875 for the optimum criterion>0.55 in predicting Pre eclampsia.

TABLE 2: COMPARISON OF SERUM CREATININE

Pre-eclampsia	Serum creatinine Mean ± STD	Mean Difference	95% CI Lower	95% CI Upper	P value
YES	0.856 ± 0.215	0.30	0.21715	0.38085	<0.001
NO	0.557 ± 0.144				

The mean of serum creatinine among people with preeclampsia was 0.856 ± 0.215 and the mean serum creatinine among people without preeclampsia was 0.557 ± 0.14in the study population. Hence Serum Creatinine was 0.30 units higher (95% CI 0.21 to 0.38, p value <0.001) in people with preeclampsia (Table 2)



ROC curve

Area under the ROC curve (AUC)	0.875313
Standard Error[a]	0.0387
95% Confidence interval[b]	0.782484 to 0.938622
z statistic	9.692
Significance level P (Area=0.5)	<0.0001

From Diagram 2, we derive that serum crystatin C has got 82.5% sensitivity and Specificity 85.0% ,Area under curve is 0.875313 for the optimum criterion>0.6 in predicting Pre eclampsia.

Discussion

Pre-eclampsia, a syndrome characterized by hypertension, proteinuria and systemic vasoconstriction, is one of the leading causes of maternal and fetal morbidity. Although the exact etiology of pre-eclampsia is not clear, insufficient placental function is thought to play a pivotal role. Studies have shown the association of pre-eclampsia with deficiency in the trophoblast invasion of maternal spinal arteries, leading to poor perfusion of feto-placental unit. Cathepsins (cysteine-proteases) are considered to be important for trophoblast invasion while their inhi-bitor, cystatin C, regulates this invasion to prevent formation of placenta accreta or percreta.

A study concerning serum levels of cystatin C in preeclampsia and normal pregnancy was published by Strevens et al[48]. These investigators have found serum cystatin C concentrations to be significantly elevated in preeclamptic patients compared to normal pregnant women.

Our data regarding both cystatin C and creatinine levels are consistent with the previous studies of Shalvi Sharma et al[19] and Fauzia Jumaat et al. Karl Kristensen[21] et al, which showed elevated plasma concentrations of cystatin C in patients with preeclampsia at the time of diagnosis.

In our study, the mean age group, gestational age and parity of both controls and cases was similar. Serum cystatin C concentrations were significantly higher in pre-eclamptic patients (0.895 ±0.310mg/L) compared to the healthy pregnant females (0.489 ± 0.064 mg/L) with p value of <0.001 (highly significant). Serum levels of cystatin C are increased in normal pregnancy, especially in the third trimester.

The levels of Cystatin C are further increased in pre-eclampsia, correlating with the functional and structural changes in kidneys.

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. The Area under curve values confirm the observations of Cystatin C being superior to serum creatinine for prediction of pre-eclampsia patients.

Conclusion:

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

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