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Utility of Cystatin C in Assessing Glomerular Filtatration Rate in Pregnant Women with Preeclampsia

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Abstract

Background and Objectives: Preeclampsia is a hypertensive disorder of pregnancy associated in the second Trimester of the pregnancy characterized with recent-onset of hypertension and accompanying proteinuria. It affects nearly 5% of all pregnancies, producing substantial maternal and perinatal morbidity and mortality. Kidney injury is one of the complications of preeclampsia complicating the management. Therefore this study intended to find the utility of estimating cystatin C in preeclampsia patients.

Material & Methods: 42 preeclampsia patients and equal number of age and gestation age matched normal pregnant women were enrolled for the study. Blood pressures were measured and mean blood pressure values were recorded. Serum cystatin C and creatinine were estimated. Estimated GFR was calculated using MDRD equation. All the observations were tabulated and analysed statistically using software.

Results: Cystatin C in pregnant women with preeclampsia and in normal pregnant women was found to be 0.91±0.22 and 0.56±0.16 mg/dl respectively. The difference was statistically significant ($p<0.01$).Serum cystatin C levels significantly correlated with blood pressure, serum creatinine levels and eGFR values.

Conclusion: Thus, cystatin C can be utilised to assess the renal function in preeclampsia complicated pregnancy.

Keywords: cystatin c; Preeclampsia; Pregnancy; Renal marker.

Introduction

Preeclampsia is a hypertensive disorder of pregnancy developing in the second half (≥20 weeks) of the pregnancy characterized with new-onset hypertension (BP≥ 140/90 mm Hg) and proteinuria (urinary albumin ≥ 300 mg/24 hr) as the prime characteristics [1]. Preeclampsia has a prevalence of 5-8% of pregnancies worldwide and a much higher rate of prevalence in India varying with the demographic location, and is the second leading cause of direct maternal deaths [2].

Kidney injury is one of the serious complications associated with preeclampsia [3]. In preeclampsia, both glomerular filtration rate (GFR) and renal plasma flow decrease by 30% to 40% compared with normal pregnancy of the same duration [4]. Prolonged renal hypoperfusion can result in acute tubular necrosis that is seen with severe preeclampsia [5]. Presently, GFR is calculated using the serum creatinine value and urinary creatinine levels present in the 24 hour urinary sample. Alternately, estimated GFR (eGFR) is calculated using the formulas like The *Cockcroft* and

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Gault *formula* and The Modification of Diet in Renal Disease (MDRD) equation. Therefore, there is a need of a parameter that can be easily estimated and quantified to identify the kidney injury in terms of the compromise on the glomerular filtration.

Cystatin C is a low molecular weight, basic neuroendocrine polypeptide encoded by CST3 gene cystatin C. It is one of the most important extracellular inhibitors of cysteine proteases and a potent inhibitor of lysosomal proteases. It is expressed ubiquitously and can be found in various biological fluids including serum [6]. It is removed from the bloodstream by glomerular filtration by the kidneys. Conditions associated with the compromise in the renal function are found to be associated with increased cystatin levels in blood [7].

Though estimation of cystatin C is practised to assess the GFR in kidney injury due to various causes like diabetic and hypertensive nephropathy, it is not used to assess GFR in preeclampsia. Also, there are limited studies on estimation of cystatin C in Indian pregnant population. Therefore, this study was undertaken to find the serum levels of cystatin C in preeclampsia patients compared to normal pregnant women.

Materials and Methods

This case control study was conducted in the MS Ramaiah Medical College, Bangalore. Cases included 42 preeclampsia patients admitted in the M S Ramaiah Hospital. Controls include 42 normotensive, healthy women attending the outpatient department at MS Ramaiah Hospital for their antenatal checkups. This sample size was calculated with an expectation to get a result with 80% power, 95% confidence and minimum detectable difference between the two groups as 0.095 mg/l. It was determined to require a minimum of 42 subjects in each group. This study was carried out after obtaining the approval from the institutional ethics committee. Informed consent was obtained after explaining the nature and purpose of the study from all the subjects. Clinically diagnosed preeclampsia patients were included i.e patients with ≥ 20 weeks of the pregnancy, pregnancy induced hypertension with blood pressure ≥ 140/90 mm Hg and urinary albumin ≥ 300 mg in a 24 hr sample. Pregnant women with bad obstetric history, pre existing disorders like diabetes, hypertension, thyroid disorders and any other chronic illness were excluded. Women who developed thyroid illness during the pregnancy and gestational diabetes were also excluded from the study.

About 5 ml of random blood sample was collected in a gel vacutainer and allowed to clot. This is later centrifuged to separate the serum. Serum is aliquoted in ependorff tubes and stored at -20°C. Serum cystatin C and creatinine were estimated on an autoanalyser (Roche – cobas ® 6000 System) by turbidimetry and modified Jaffe's method respectively. Estimated Glomerular filtration rate (eGFR) was calculated by MDRD equation using an online calculator. A serum cystatin C level was presented in terms of mean with standard deviation and descriptive statistical analysis was performed using SPSS version 20.

Results

This case-control study included 42 patients with preeclampsia and 42 normal pregnant women. Both the cases and the controls were aged between 19 to 35 years. The mean age was 25.12 ± 3.62 and 26.62 ± 3.46 years for controls and cases respectively. Seventy five percent of the controls and 66% of preeclampsia subjects were primigravida. The results obtained were tabulated and analysed. This study observed that patients with preeclampsia had significantly raised cystatin C levels ($p < 0.01$) compared to normal pregnant women (Table 1). The cystatin C levels showed correlation with mean blood pressure readings in preeclampsia subjects. It also showed significant correlation with other parameters of kidney injury namely serum creatinine and eGFR.

Table 1: Shows the Mean ± Sd of the Various Parameters

Parameters	Cases	Controls	p Value*
Age (years)	26.62 ± 3.46	25.12 ± 3.62	0.16
Gestational age (weeks)	32.33 ± 3.01	33.29 ± 4.77	0.28
Systolic Blood pressure (mmHg)	145.14 ± 13.62	114.95 ± 7.00	<0.01
Diastolic Blood pressure (mmHg)	96.62 ± 8.19	72.62 ± 6.27	<0.01
Serum Creatinine (mg/dl)	0.86 ± 0.15	0.80 ± 0.11	<0.05
Estimated GFR (Calculated)	97.00 ± 19.16	104.71 ± 16.15	<0.05
Serum Cystatin C (mg/L)	0.91 ± 0.22	0.56 ± 0.16	<0.01

*p<0.01 - Highly significant; p<0.05 – Significant; p>0.05 - Not significant

Table 2: Shows the Pearson's Correlation between Various Parameters

	Age	Gestational age	Systolic Blood pressure	Diastolic Blood pressure	Serum Creatinine	Estimated GFR	Serum Cystatin C
Age		r=0.28 p=0.07	r=0.10 p=0.52	r=0.11 p=0.48	r=0.50 p=<0.01	r=-0.60 p=<0.01	r=0.38 p=0.01
Gestational age	r=0.28 p=0.07		r=0.13 p=0.41	r=0.11 p=0.48	r=0.09 p=0.57	r=-0.11 p=0.48	r=0.25 p=0.11
Systolic Blood pressure	r=0.10 p=0.52	r=0.13 p=0.41		r=0.38 p=0.01	r=0.55 p=<0.01	r=-0.41 p=<0.01	r=0.40 p=<0.01
Diastolic Blood pressure	r=0.11 p=0.48	r=0.11 p=0.48	r=0.38 p=0.01		r=0.48 p=<0.01	r=-0.44 p=<0.01	r=0.41 p=<0.01
Serum Creatinine	r=0.50 p=<0.01	r=0.09 p=0.57	r=0.55 p=<0.01	r=0.48 p=<0.01		r=-0.97 p=<0.01	r=0.41 p=<0.01
Estimated GFR	r=-0.60 p=<0.01	r=-0.11 p=0.48	r=-0.41 p=<0.01	r=-0.44 p=<0.01	r=-0.97 p=<0.01		r=-0.40 p=<0.01
Serum Cystatin C	r=0.38 p=0.01	r=0.25 p=0.11	r=0.40 p=<0.01	r=0.45 p=<0.01	r=0.41 p=<0.01	r=-0.40 p=<0.01	

r - Pearson's correlation co-efficient; p<0.01 - Highly significant; p<0.05 – Significant; p>0.05 - Not significant

Discussion

Because of its wide spread systemic involvement preeclampsia has the potential to produce significant maternal and foetal complications. Acute kidney injury is one of the complications in preeclampsia that compounds the difficulty in treatment of the patient with preeclampsia [8]. Currently the procedures in vogue to measure GFR are not clear and there is a need for an analyte that can be estimated easily, cost effective and interpreted. Cystatin C has been established as a simple and endogenous marker for GFR in clinical nephrology [9]. Utility of cystatin C for detection of renal impairment in preeclampsia women is not well established. Therefore, present study intended to determine the serum cystatin C values in preeclampsia and normal pregnant women and to compare with serum creatinine and eGFR.

This case-control study with 42 patients with preeclampsia and 42 normal pregnant women showed significantly increased cystatin C levels ($p< 0.01$) in pregnant women with preeclampsia. In normal pregnancy, renal plasma flow increases by 40% to 60% resulting in increased GFR [10]. In preeclampsia, both GFR and renal plasma flow decrease by 30% to 40% compared with normal pregnancy of the same duration [11]. Cystatin C in the plasma is removed from the bloodstream by glomerular filtration. It accumulates in preeclampsia due to decreased renal plasma flow and compromised GFR [12]. Thus, cystatin C concentrations increase in blood. This study also showed that cystatin C levels significantly correlated with blood pressures, serum creatinine and eGFR, thus indicating that cystatin C concentrations is in accordance with the existing parameters. Franceschini N et al. not only showed elevated cystatin C levels in preeclampsia cases compared with controls but also showed 12 fold rise for the fourth quartile patients who were distributed based on adjusted odds ratios and 95% confidence intervals [13]. Strevens D et al. performed receiver operating characteristic analysis between cystatin C and serum creatinine. They demonstrated that the serum level of cystatin C had a superior diagnostic accuracy for preeclampsia compared to serum creatinine [14]. Thus cystatin C can be a useful parameter to assess the kidney injury in preeclampsia complicated pregnancy.

Conclusion

Cystatin C levels are raised in the pregnant women with preeclampsia compared to normal pregnant women. Hence, it can be a useful parameter to assess glomerular filtration rate to identify the kidney injury in pregnant women with preeclampsia.

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