Serum and urine cystatin C as renal markers of preeclampsia

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Serum and urine cystatin C as renal markers of preeclampsia

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The Master's Thesis submitted to
the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of
Master of Medical Science

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December, 2008

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December 2008

ACKNOWLEDGEMENT

I would like to sincerely thank and give my deepest appreciation to professor Dong Jae Cho, and professor Yong Won Park for not only being my thesis supervisor but being my true mentor throughout my OBGYN residency and fellowship. I could not have come this far without their guidance.

I would also like to thank Professor Jeong-Ho Kim for giving me endless advice and support.

Special thanks to all the first year residents and all the nurses in the labor and delivery room who helped me gather samples from the participants. I could not have completed my thesis without their help and support.

Finally, I would like to thank my family especially Joon Woo who keeps me sane.

Soo Jin Lee

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<ABSTRACT>

Serum and urine cystatin C as renal makers of preeclampsia

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An altered renal function is an essential component of the pathophysiology of preeclampsia and close monitoring of renal function is essential to ascertain the optimal time of delivery. Given the critical role of acute kidney injury in the pathogenesis of preeclampsia, both serum and urine cystatin C (CysC) were investigated as markers of renal function in preeclampsia.

The serum and urine levels of CysC were determined in 22 patients with preeclampsia and 44 gestational age-matched pregnant women by particle-enhanced immunoturbidimetric assays. Comparatively, serum creatinine, serum urea nitrogen, serum uric acid, and urine creatinine concentrations were determined in each sample.

Compared to controls, serum concentrations of CysC (1.10 ± 0.28 vs. 0.76 ± 0.20 mg/dL, $p<0.001$), creatinine (0.73 ± 0.13 vs. 0.61 ± 0.10 mg/dL, $p<0.001$), urea nitrogen (12.14 ± 7.16 vs. 7.16 ± 2.27 mg/dL, $p<0.001$), and uric acid (6.32 ± 1.05 vs. 3.69 ± 0.66 mg/dL, $p<0.001$) were significantly higher, and the estimated glomerular filtration rate (eGFR) (100.63 ± 20.3 vs. 125.72 ± 25.36 ml/min/1.73m^2, $p<0.001$)

determined by Modification of Diet in Renal Disease (MDRD) formula significantly lower in preeclampsia group. However, the urine CysC level was not significantly different between preeclampsia and control group (0.12 ± 0.14 vs. 0.07 ± 0.22 mg/dL, p=0.44). A significant positive correlation was found between serum CysC and the following serum levels: uric acid (r=0.73, p< 0.01), urea nitrogen (r=0.61, p< 0.05), and creatinine (r=0.71, p<0.01); whereas a negative correlation was found beween serum CysC and eGFR (r=-0.63, p<0.01). Serum CysC had the highest AUC compared to other analytes for identifying preeclampsia when the cutoff level was 0.885 mg/dL (AUC: 0.977, [95% CI: 0.945-1.010], p<0.001, sensitivity and specificity 86.4%, and 81.1%), and the odds ratio was 5.74 ([95% CI: 1.98-16.67], p<0.001).

Our data showed that serum CysC but not urine CysC could be used as a marker of impaired renal function in preeclampsia. Furthermore, our results demonstrated that serum CysC could serve as an adjunct to other clinical markers for increasing surveillance for preeclampsia.

Key words: cystatin C, urine, preeclampsia

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I. INTRODUCTION

Preeclampsia affects 5-7% of all pregnancies and is a leading cause of maternal and perinatal morbidity and mortality.[1] The condition is characterized by hypertension, proteinuria and a generalized systemic vasoconstriction arising from circulatory disturbances secondary to generalized endothelial dysfunction.[2] The degree of hypertension and proteinuria are poor prognostic factors for maternal and fetal outcome and better diagnostic markers are need.[3] Although numerous biochemical markers have been studied for the prediction of preeclampsia, as of yet, there is no reliable marker for the disease.[4]

Alteration in the renal function is an essential component of the pathophysiological process in preeclampsia and close monitoring of renal function is essential to ascertain the optimal time of delivery. The serum levels of creatinine and uric acid have been used to monitor renal function in preeclampsia with limitations.[5, 6] Recent studies have shown that serum cystatin C (CysC) in pregnancy is closely correlated to glomerular filtration rate (GFR) in both nonpregnant and pregnant hypertensive women.[7, 8] The serum level of CysC is increased in pregnancy and even more so in preeclampsia, which is closely correlated to functional and structural changes in the kidneys.[9, 10] In

addition, placental expression of CysC is increased in preeclampsia which could contribute to the elevated maternal plasma levels observed in preeclampsia.[11]

CysC, a nonglycosylated 13-kDa protein, is an endogenous marker of renal function because it is exclusively eliminated from the circulation by glomerular filtration. It functions as a cysteine proteinase inhibitor involved in the intracellular catabolism of proteins and produced at a constant rate by nucleated cells.[12] Because of its low molecular weight and its positive charge, CysC is freely filtered by the renal glomeruli and almost completely absorbed and catabolized in the renal proximal tubular cells.[13] Serum CysC concentration show no relation to muscle mass, body height, and gender, and are unaffected by infection, hyperbilirubinemia and a wide variety of extrarenal disorders.[14, 15]

Previous studies have mainly concentrated on comparing serum CysC and of serum creatinine as parameters of GFR. However, little attention has been focused on urinary CysC excretion rates, probably due to its low concentrations in urine.[12] Urine concentration of CysC is low, and its concentration in normal subjects is about 100 *u*g/l. There have been several reports of significantly increased excretion of urinary CysC in adults with decreased creatinine clearance.[16,17] Increased urinary CysC was noted especially in renal disorders such as the tubular damage associated with Chinese herbs, HIV nephropathy, and acute interstitial nephrities.[18-20] In a different study, urinary excretion of CysC accurately predicted the requirement of renal replacement therapy in patients with acute tubular necrosis.[21] Despite its low concentration in urine, there have been reports stating that measurement of urine CysC is highly accurate and precise with commercially available, automated nephelometric assay.[22]

Given the critical role of acute kidney injury in the pathogenesis of preeclampsia, we wanted to investigate both serum and urinary CysC as markers of renal function in preeclampsia. Detecting patients at increased risk for preeclampsia by using urinary CysC, a less invasive method, may help early

supportive care or to initiate potential future therapeutic interventions which may consequently improve the maternal and fetal outcome of preeclampsia.

II. MATERIALS AND METHODS

1. Subjects

The study was performed during a 5 months period from April 2008 to September 2008. We included 44 uncomplicated normal singleton pregnancies and 22 pregnant women diagnosed with preeclampsia delivered at the Department of Obstetrics and Gynecology, Yonsei University Health System. All pregnancies were dated according to routine ultrasound measurements at 17-18 weeks of gestation. Women with pre-pregnancy diabetes, hypertension or chronic renal disease were excluded.

Pre-eclampsia was defined as follows: a systolic and diastolic blood pressure of ≥ 140 and ≥ 90 mmHg, respectively, and proteinuria defined as ≥ 300 mg protein in a 24-h urine specimen or ≥ 1+ protein by dipstick urine sample after 20 weeks of gestation in a woman with previously normal blood pressure.

Severe preeclampsia was diagnosed when the diastolic blood pressure was 110 mmHg or higher and when the dipstick urine was 2+ or more, or protein in a 24-hr urine collection was 2 g or more following the criteria set by the National High Blood Pressure Education Program Working Group Report on High Blood Pressure in Pregnancy (2000). All the participants in preeclampsia group were in the severe preeclampsia group.

2. Sampling

On admission to our institution, venous blood samples were collected, centrifuged at 3500 rpm (2000g) for 10 minutes and frozen at -80℃ in aliquots and stored for later analysis. Spot urine samples (3ml) were collected in duplicates and stored -80℃ for subsequent determination of CysC. All subjects gave informed consent to the collection and use of urine and serum samples.

3. Methods

(1) Determination of serum and urine CysC, serum creatinine, serum urea nitrogen, and serum uric acid.

Serum creatinine was measured using a Jaffe kinetic reaction on a Hitachi 7600 Clinical Analyzer with reagents obtained from Daiichi Pure Chemicals Co. Ltd., (Tokyo, Japan) in accordance with the procedure recommended by the reagent producer.

Serum uric acid was measured using an enzymatic method on a Hitachi 7600 Clinical Analyzer with reagents obtained from Daiichi Pure Chemicals Co. Ltd., in accordance with the procedure recommended by the reagent producer.

Serum urea nitrogen was measured using an enzymatic method on a Hitachi 7600 Clinical Analyzer with reagents obtained from Wako Pure Chemical Industries, Ltd., (Osaka, Japan) in accordance with the procedure recommended by the reagent producer.

Undiluted serum and urine CysC were measured using an automated particle-enhanced immunoturbidimetric method on Advia 1650 (New York, USA) with HiSens® Cystatin-C LTIA Reagent (HBI Co., Ltd, Kyunggi-do, Korea) in accordance with the procedure recommended by the reagent producer. The total coefficient of variation was 10 % at a standard CysC concentration of 0.4 mg/L. The assay was originally designed for serum CysC analysis and has a lower limit of dectection of 0.32 mg/dL**.** The lower limit of detection for urine CysC was not available for the assay, however, in our urine specimens, the lowest detectable concentration of urine CysC was 0.01 mg/dL and any urine values lower or undetected by the assay were represented as 0.005 mg/dL.

(2) Determination of estimated glomerular filtration rate (eGFR)

eGFR was calculated using the Modification of Diet in Renal Disease

(MDRD) formula.[23, 24]

4. Statistical analyses

Differences between the two groups were tested with Student t-test and χ^2 test as appropriate. Association between variables was assessed with Pearson and Spearman correlation coefficient as appropriate. The diagnostic performance of serum CysC, serum uric acid, serum creatinine, and serum urea nitrogen to detect preeclampsia was evaluated by ROC analysis. Sensitivities and specificities were calculated at the optimum cut-off level. The AUCs were compared pairwise.[25] P value less than 0.05 was considered significant. The statistical software SPSS 11.0 (SPSS Inc., Chicago IL, USA) was used for all the calculations.

III. RESULTS

1. Clinical characteristics of preeclampsia and control group.

The clinical characteristics of preeclampsia and control group are shown in Table 1. Overall, there was no significant difference in gestational weeks at admission, maternal age, parity, weight, height, and body mass index (BMI) between the two groups. Preeclampsia group had significantly higher systolic and diastolic blood pressure at admission compared to control group.

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Table 1. Clinical characteristics of preeclampsia and control group.

	Preeclampsia (n=22)	Control (n=44)	*P* value
Sampling Week (wks)	33.5±5.7	33.7±5.1	0.85
Maternal Age (yrs)	32.9±3.1	31.1±3.9	0.06
Parity	0.45±0.59	0.50±0.63	0.78
Systolic BP (mmHg)	159.2±14.9	115.4±9.8	<0.001
Diastolic BP (mmHg)	98.3±10.1	71.1±9.6	<0.001
Weight (Kg)	69.6±12.8	64.1±7.8	0.07
Height (cm)	160.0±6.7	159.9±5.2	0.9
BMI (Kg/m^2)	27.3±5.4	26.5±2.9	0.08

Data: mean ± SD

2. Laboratory parameters between preeclampsia and control group.

The serum and urine concentrations of all analytes are shown in Table 2. The serum concentrations of CysC (1.10 ± 0.28 vs. 0.76 ± 0.20 mg/dL, $p<0.001$), uric acid (6.32 ± 1.05 vs. 3.69 ± 0.66 mg/dL, $p<0.001$), creatinine (0.73 ± 0.13 vs. 0.61 ± 0.10 mg/dL, $p<0.001$), and urea nitrogen (12.14 ± 7.16 vs. 7.16 ± 2.27 mg/dL, $p<0.001$) were all significantly higher, and the eGFR significantly lower in preeclampsia group. However, the urine concentrations of CysC, creatinine, and CysC- to-creatinine ratio did not differ significantly between the two groups.

Table 2. Laboratory parameters of preeclampsia and control group

	Preeclampsia (n=22)	Control (n=44)	*P* value
Serum urea nitrogen (mg/dL)	12.1±4.3	7.2±2.3	<0.001
Serum creatinine (mg/dL)	0.7±0.1	0.6±0.1	<0.001
Serum uric acid (mg/dL)	6.3±1.0	3.7±0.7	<0.001
Serum CysC (mg/dL)	1.10±0.28	0.76±0.20	<0.001
Urine CysC (mg/dL)	0.12±0.14	0.07±0.21	0.44
Urine creatinine (mg/dL)	105.0±79.6	68.8±43.9	0.06
Urine CysC/Cr (x 10^{-3})	1.31±1.5	0.98±0.24	0.06
eGFR (ml/min/1.73m^2)	100.6±20.3	125.7±25.4	<0.001

Data: mean ± SD

3. Correlation among the analytes.

The serum level of CysC was correlated to gestational weeks (r=0.37), serum uric acid (r=0.73), serum creatinine (r=0.71), and serum urea nitrogen (r=0.61) according to the Pearson correlation coefficient. The correlation coefficient between serum CysC and the degree of proteinuria (r=0.60) was found using the Spearman correlation. The serum CysC level and eGFR (r=-0.63) were inversely correlated. All association were significant at the $p<0.001$ level. No significant correlation was shown between serum and urine CysC.

Table 3. Correlation coefficient among serum cystatin C and other variables

	Correlation Coefficient (*r*)	*P* value
Gestational weeks	0.37	<0.001
Proteinuria	0.60†	<0.001
Urine Creatinine	0.28	0.045
Serum uric acid	0.73	<0.001
Serum urea nitrogen	0.61	<0.001
Serum creatinine	0.71	<0.001
eGFR	-0.63	<0.001
Urine CysC	0.12	0.3

†: Spearman correlation coefficient

r: Pearson correlation coefficient.

4. Diagnostic performance of serum cystatin C, serum uric acid, serum creatinine, and serum urea nitrogen as markers of preeclampsia.

To evaluate the discriminative capacity of each serum analyte to detect preeclampsia, ROC analysis was performed using the data from both groups, and the results are summarized in Figure 1, and Table 4. Based on the area under the curves (AUC) as shown in Table 4, serum CysC had a superior diagnostic accuracy for preeeclampsia than serum uric acid, serum creatinine, and serum urea nitrogen ($p<0.001$). The AUCs of serum uric acid, serum creatinine, and serum urea nitrogen did not reach statistical significance. The clinical cut off level was calculated at the value with the highest accuracy (highest sensitivities and specificities combined).

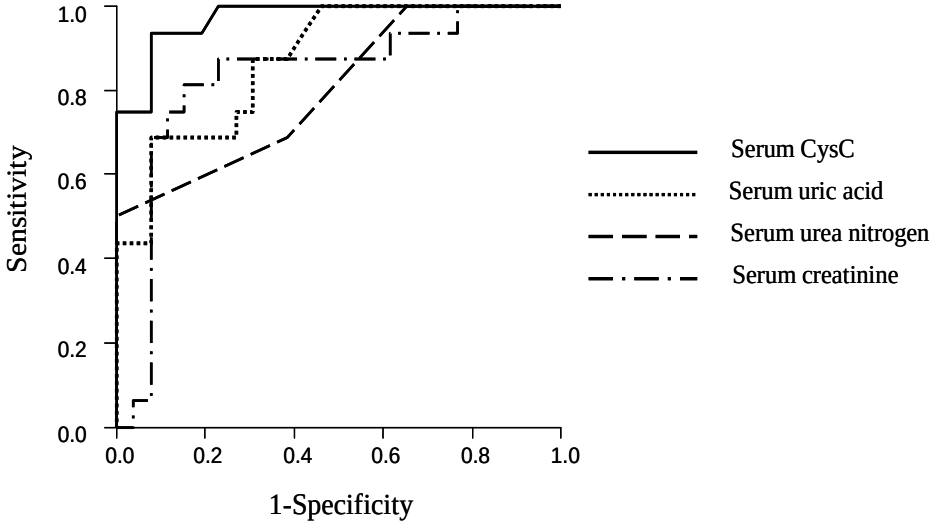

Figure 1. ROC curves for serum CysC (AUC: 0.977, [95% CI: 0.945-1.010]), serum uric acid (AUC: 0.863, [95% CI: 0.812-0.940]), serum urea nitrogen (AUC: 0.768, [95% CI: 0.750-0.924]), and serum creatinine (AUC: 0.861, [95% CI: 0.689-0.939]) as markers of preeclampsia. The curves were compared to each other pairwise. Serum CysC had a significantly larger AUC than serum uric acid, serum creatinine, and serum urea nitrogen ($p<0.001$). The AUCs of serum uric acid, serum creatinine, and serum urean nitrogen did not reach statistical significance.

Table 4. Diagnostic performance of serum cystatin C, serum uric acid, serum creatinine, and serum urea nitrogen for identifying preeclampsia

	AUC	Cutoff (mg/dL)	Sensitivity	Specificity	PPV	NPV	OR [95% CI]
Serum CysC	0.978*	0.885	86.4%	81.1%	70.4%	90.6%	5.74 [1.98-16.67]
Serum uric acid	0.863	4.65	84.4%	80.3%	81.3%	87.1%	3.6 [3.05-10.5]
Serum Creatinine	0.861	0.75	50.0%	94.3%	87.5%	80.5%	2.59 [1.48-4.53]
Serum urea nitrogen	0.768	10.55	68.2%	94.3%	88.2%	82.5%	2.96 [1.59-5.49]

* Serum CysC had a significantly larger AUC than serum uric acid, serum creatinine, and serum urea nitrogen ($p<0.001$) (pair-wise comparison)

AUC: area under the curve;

PPV: positive predictive value;

NPV: negative predictive value;

OR: odds ratio.

IV. DISCUSSION

Cystatin C is a basic protein, freely filtered by the glomerulus, and completely reabsorbed by the proximal tubular cells.[12] Recent studies have shown that serum CysC in pregnancy is closely correlated to GFR in both nonpregnant and pregnant hypertensive women.[7, 8] The serum level of CysC is increased in pregnancy and even more so in preeclampsia, which is closely correlated to the degree of endotheliosis and the changes in the glomerular volume.[9, 10] Furthermore, Strevens et al., demonstrated that serum CysC had a superior diagnostic accuracy for preeclampsia compared to those of uric acid and creatinine.[5]

In our study, the mean serum levels of CysC, uric acid, creatinine and urea nitrogen were significantly higher in preeclampsia group compared to control group, whereas there was no significant difference in the urine CysC concentration between the two groups. However, although uric acid and creatinine concentrations were increased in preeclampsia group, the levels were not above the corresponding upper reference limits for normal term pregnancy, which reduces the usefulness of the variables for monitoring preeclamptic women.

Several explanations have been given for the increase in serum CysC concentration in preeclampsia. First, although GFR is normally increased during pregnancy, preeclampsia is characterized by a decrease in GFR, which could lead to decrease in renal filtration of CysC.[26] Another possible explanation might be that some abnormal renal processes in preeclampsia might affect the filtration of CysC differently. For example, glomerular endotheliosis which is more pronounced in preeclampsia might cause a decrease in the glomerular pore size, in the number of pores, or in the number of anionic sites in the glomerular barrier which could affect the filtration of positively charged low molecular mass proteins like CysC.[10] Recently, injury and depletion of podocytes in the glomerular basement membrane leading to podocyturia has been described.[27] Therefore, high CysC levels likely reflect renal dysfunction in preeclampsia. Finally, Kristensen et al., demonstrated increased placental expression and secretion of CysC which

could also contribute to the elevate serum levels in preeclampsia.[11] CysC is known to be expressed in most human tissues including kidney, liver, pancreas, intestine, stomach, lung and placenta, an increased expression in cells outside the placenta could also contribute to the elevated circulatory levels seen in preeclampsia.[28]

The nature of the renal lesions in preeclampsia is uncertain. Previous studies of the composition of the urinary proteins have led to the conclusion that proteinuria of preeclampsia is attributable entirely to increased glomerular permeability with little evidence of defective tubular reabsorption. In recent years more sensitive indicators of renal tubular dysfunction have become available including β2-microglobulin and CysC. A previous study by Krieger et al., demonstrated increased urinary excretion of β2-microglobulin in preeclampsia indicating presence of renal tubular lesions in the absence of detectable proteinuria.[28] Other studies have evaluated different urinary biochemical parameters such as N-acetyl-β-D-glucosaminidase, total protein, albumin, urea nitrogen, uric acid, and creatinine in women with preeclampsia reflecting different abnormalities of renal glomeruli and tubules.[30]

Being noninvasive, urine test would be superior to one that requires a blood sampling. In our study, we evaluated urine CysC in preeclampsia to determine its role as a marker of renal damage and proteinuria in preeclampsia since urinary CysC concentrations have not been widely studied. However, we were not able to find any significant difference in the concentration of urine CysC between preeclampsia and control group. The underlying pathophysiology for this insignificant difference in urine CysC concentration needs to be further evaluated. Possible explanations are decrease in GFR leading to decrease in renal filtration of CysC in preeclampsia,[26] and abnormal renal dysfunction such as glomerular endotheliosis occurring in preeclampsia ultimately leading to hypofiltration of CysC. Such hypofiltration of CysC could lead to even lower levels of CysC in urine to be detected with accuracy.

Several important limitations to our study exist. One important limitation to our

study is the failure to compare our data with the standard measurement of GFR such as inulin clearance. Instead we used eGFR using the MDRD formula.[23, 24] Another important limitation lies in the cross sectional study design. In particular, future studies should address if CysC levels vary with the severity of preeclampsia and the degree of renal damage since all the patients in our preeclamptic group fall into the "severe" preeclampsia group. Prospective cohort studies are needed to clarify the temporal relation between alteration in CysC concentrations and the occurrence of preeclampsia, and to determine whether elevated CysC concentrations in the early pregnancy are predictive of poor maternal and fetal outcomes in preeeclampsia.

In conclusion, ROC analysis of our data demonstrates that serum CysC has a superior diagnostic accuracy for preeclampsia compared to that of serum uric acid and serum creatinine.

. Although high blood pressure and proteinuria is regarded as the simples and most useful markers of the development of preeclampsia, blood pressure levels are variable, and proteinuria can be absent, even with other ominous features of preeclampsia.[31] Serum CysC, reflecting GFR, is an indicator of different aspect of renal features of preeclampsia, and could thereby be helpful in the diagnosis of preeclampsia and possibly indicate the severity of disease.

V. CONCLUSION

The results of the present study show that serum CysC levels in women with preeclampsia were higher than the normal pregnant group whereas urine CysC did not differ significantly between the two groups. The mechanism for the insignificant difference in the urine CysC concentration remains insufficiently understood. Serum CysC in our study significantly correlated with serum creatinine, serum uric acid, and eGFR.

There was a linear relationship between serum CysC and GFR similar to serum creatinine, but unlike creatinine, CysC is unaffected by extrarenal factors such as age, muscle mass, hydration status, anemia, or infection. Renal impairment is a commom feature of preeclampsia, and our study indicates that low molecular mass serum proteins such as CysC could be useful markers of renal impairment in preeclampsia.

Further prospective studies are needed in order to determine if serum CysC may be used in preeclamptic pregnancy as a reliable endogenous marker for kidney function so that it may provide an earlier diagnosis of acute kidney injury.

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< ABSTRACT (IN KOREAN)>

임신중독증 산모에서 혈청 및 요중 cystatin C의 신기능 지표로서의 의의

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임신성 고혈압은 모체와 태아 모두에 치명적인 결과를 초래할 수 있는 임신 중, 후반기의 합병증으로 산모의 주요 장기에 다양한 합병증을 유발한다. 특히 신장은 그 병태생리 및 전자간증의 고전적인 triad-고혈압, 단백뇨, 부종-에서 알 수 있듯이 가장 영향을 받는 기관의 하나로 산모의 치료 및 장기적인 예후에 있어서 중요한 역할을 수행한다. 따라서 본 연구에서는 임신중독증 산모에서 신기능의 척도로 cystatin C (CysC)의 역할을 살펴보고자 하였다.

2008년 5월부터 2008년 9월 사이에 연세의료원 산부인과에 내원하여 분만한 22명의 임신중독증 산모와 44명의 정상 산모를 대상으로 혈청 및 요 CysC, 혈청 요산, 혈청 creatinine, 그리고 혈청 urea nitrogen을 측정하여 두 군을 비교하였다. 이후 Pearson 상관분석으로 변수간의 상관계수를 구하였으며 ROC curve를 통해 임신중독증을 예측할 수 있는지 검토하였다.

임신중독증 군이 정상 산모군에 비하여 혈청 CysC (1.10 ± 0.28 vs. 0.76 ± 0.20 mg/dL, p<0.001), 요산 (6.32 ± 1.05 vs. 3.69 ± 0.66 mg/dL, p<0.001), creatinine (0.73 ± 0.13 vs. 0.61 ± 0.10 mg/dL, p<0.001), urea nitrogen (12.14 ± 7.16 vs. 7.16 ± 2.27 mg/dL, p<0.001) 이 모두 유의하게 높았으며, 사구체 여과율 (100.63 ± 20.3 vs. 125.72 ± 25.36 ml/min/1.73m^2, p<0.001)은 유의하게 낮았다. 반면에 두 군간에 요중 CysC의 유의한 차이는 없었다. 혈청 CysC는 요산 (r=0.73), creatinine (r=0.71), urea nitrogen (r=0.61), 사구체 여과율 (r=-0.63)과 높은 상관성을 보였다. 임신중독증을 예측할 수 있는 진단적 정확도는 ROC curve 상에서 아래 영역 면적율을 측정하여 비교한 결과 CysC가 0.977로 가장 높았다 ([95% CI: 0.945-1.010], p<0.001). 설정된 혈청 CysC 참고치를 적용하여 임신중독증을 예측할 민감도는 86.4%, 특이도는 81.1%였다.

본 연구 결과를 토대로 혈청 CysC는 임신중독증 산모의 신기능 저하 및 신손상을 검출하는데 도움이 되리라고 본다. 향후 전향적인 연구를 통하여 임신중독증을 예측하는 표지자로서의 유용성에 대해 검증해 볼 수 있으리라 본다.

핵심되는 말: Cystatin C, 임신중독증, 신기능