ORIGINAL ARTICLE

The application of serum cystatin C in estimating the renal function in women with severe preeclamptic toxemia

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KEYWORDS
Pregnancy;
Preeclampsia;
Cystatin C

Abstract
Introduction: Preeclampsia is a medical condition where hypertension arises in association with significant amount of proteinuria. It appears likely that there are substances from the placenta that can cause endothelial dysfunction in the maternal blood vessels of susceptible women. Preeclampsia usually develops from 20 weeks and it is the most common of the dangerous pregnancy complications; it may affect both the mother and the fetus so the ability to predict the appearance of preeclampsia later in pregnancy would be of great value, although the only known treatment for eclampsia or advancing preeclampsia is delivery. Early prediction of the complication will allow close monitoring and early intervention.

Aim: The present study aimed at evaluating the role of cystatin C in the evaluation of renal function in the severe preeclampsia.

Subjects: Twenty normal primigravidae with singleton pregnancy and another 40 with severe preeclampsia recruited from preeclamptic unit of El-Shatby Maternity University Hospital, Egypt in the third trimester of gestation with exclusion of any medical disease.

Methods: They are selected and subject to full history taking, complete clinical examination, laboratory investigation with special emphasis on serum uric acid, creatinine and serum cystatin C, obstetric abdominal ultrasound and Doppler. Results of the study were tabulated and statistically analyzed.

Results: The difference in the mean serum uric acid level (3.55 ± 0.58 versus 6.76 ± 1.06 mg/dl) was significantly higher in the preeclampsia (p = 0.001), the specificity was 100% and sensitivity of the test was 97.5%, the difference in the mean serum concentration of creatinine (1.55 ± 0.89 versus 0.66 ± 0.12) was significantly higher in preeclampsia (p = 0.001), the specificity of the test was 100% and the sensitivity was 60%.

Serum cystatin C level has a mean (0.98 ± 0.29 versus 0.70 ± 0.06) which was significantly higher in preeclampsia (p = 0.001) with a specificity 100% and sensitivity 72.5%. We found a

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positive significant correlation between serum concentration of cystatin, and PI of umbilical artery Doppler (p = 0.05). Also, a significant correlation was found between serum concentration of cystatin and both PI and RI of middle cerebral artery Doppler (p = 0.05); this indicates the relation of serum cystatin C level with the severity of preeclampsia. Therefore, the past results demonstrate that the serum cystatin C and uric acid are having a good diagnostic accuracy for renal function of preeclampsia when compared to creatinine.

**Conclusion:** This indicates that cystatin C serum levels may have a significant role as a marker of preeclampsia and alternative marker of renal function in preeclampsia even more so when used in combination with uric acid levels which is still the most accurate predictor of preeclampsia and most accurate indicator of renal function of preeclampsia.

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**PALABRAS CLAVE**

Embarazo; Preeclampsia; Cistatina C

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**Aplicación de la cistatina C en sangre para la estimación de la función renal en pacientes con toxemia preeclámptica**

**Resumen**

**Introducción:** La preeclampsia es un trastorno en el que la hipertensión aparece asociada con una proteinuria significativa. Parece probable que existan sustancias de la placenta que puedan ocasionar una disfunción endotelial en los vasos sanguíneos maternos de mujeres susceptibles. La preeclampsia se desarrolla a partir de la semana 20 y es la más habitual de las complicaciones peligrosas durante el embarazo; puede afectar tanto a la madre como al feto, de modo que la capacidad de predecir su aparición durante la gestación sería muy valiosa, si bien el único tratamiento conocido para la eclampsia o preeclampsia avanzada es el parto. La detección temprana de complicaciones permitirá un seguimiento estrecho y una intervención temprana.

**Objetivo:** El presente estudio pretende analizar el rol que desempeña la cistatina C en la evaluación de la función renal en casos de preeclampsia grave.

**Participantes:** Veinte primigravidas normales con embarazo de feto único y otras 40 con preeclampsia grave identificada en la unidad de preeclampsia del Hospital de Maternidad El-Shatby durante el tercer trimestre de gestación y con exclusión de otras enfermedades previas.

**Métodos:** Se escogieron las participantes y se elaboró la historia, exploración clínica completa, análisis de laboratorio con especial hincapié en los valores de ácido úrico, creatinina y cistatina C en sangre, ecografía obstétrica abdominal y doppler. Los resultados del estudio se tabularon y analizaron estadísticamente.

**Resultados:** La diferencia en los niveles medios de ácido úrico en sangre (3,55 ± 0,58 frente a 6,76 ± 1,06 mg/dl) fue significativamente mayor en la preeclampsia (p = 0,001), la especificidad de la prueba fue de 100% y la sensibilidad fue de 97,5%. La diferencia en la concentración media de creatinina (1,55 ± 0,89 frente a 0,66 ± 0,12) fue significativamente mayor en la preeclampsia, la especificidad de la prueba fue de 100% y la sensibilidad fue de 60%. El valor de cistatina C fue de media (0,98 ± 0,29 frente a 0,70 ± 0,06) significativamente mayor en la preeclampsia (p = 0,001) con una especificidad del 100% y una sensibilidad del 72,5%. Se encontró una relación significativa entre la concentración de cistatina en sangre y el IP del doppler de la arteria umbilical (p = 0,05). Asimismo, se encontró una relación significativa entre la concentración en sangre de cistatina y el IP y el IR del doppler de la arteria cerebral media (p = 0,05), lo que indica una relación del valor de cistatina C en sangre con la gravedad de la preeclampsia. Por tanto, los resultados anteriores demuestran que la cistatina C en sangre y el ácido úrico presentan una precisión diagnóstica para la función renal de la preeclampsia cuando se compara con la creatinina.

**Conclusión:** Esto indica que los niveles de cistatina C en sangre podrían desempeñar un papel significativo como marcador de preeclampsia y como marcador alternativo de la función renal en preeclampsia, aún más al combinarse con los niveles de ácido úrico, que sigue siendo el indicador más preciso de preeclampsia y de la función renal de preeclampsia.

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**Introduction**

Preeclampsia, a pregnancy-specific disease defined as the occurrence of hypertension and significant proteinuria in a previously healthy woman on or after the 20th week of gestation, occurs in about 2–8% of pregnancies.\(^1\,^2\) It is the most common medical complication of pregnancy whose incidence has continued to increase worldwide, and it is associated with significant maternal morbidity and mortality, accounting for about 50,000 deaths worldwide annually.\(^3\,^4\)

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Hyperuricemia accompanies preeclampsia; in fact, some investigation includes it as a diagnostic criterion because of the strong correlation between hyperuricemia and histological finding of (glomerular endotheliosis) on antepartum percutaneous renal biopsy, which is believed to be characteristic of preeclampsia. Moreover, a significant correlation between the renal histological severity of preeclamptic lesion and serum uric acid has been noted, to diagnose preeclampsia, a cutoff of 5.5 mg/dL is only 69% sensitive and 51% specific. Although uric acid has been suggested to be the sensitive indicator of preeclampsia, it should not be used as an indication for delivery.18–20

Like uric acid, serum creatinine, blood urea nitrogen (BUN) and creatinine clearance reflect changes in glomerular filtration rate (GFR). BUN changes are influenced by protein intake and liver function. Thus, an abnormal BUN can be related to abnormal liver function while kidney function is normal. In addition serum creatinine levels may be elevated in severe preeclampsia. A serum creatinine level of 0.8 mg/dl in pregnancy is considered abnormal.21

Because creatinine is endogenously produced and released into body fluids in a constant rate and its plasma levels are maintained within narrow limits, its level can be measured as an indicator of GFR.22

The reference interval for creatinine clearance and the plasma creatinine in healthy adults are method dependent. The individual variation will depend in part on the age, diet, gender, inflammation, muscular mass and exercise; this variation may be sustained as much as 30% and may sustain for about 12 h after strong exercise.23

Acute renal failure caused by preeclampsia alone is rare. It is acute tubular necrosis, clinically apparent renal failure is induced by coexisting hemorrhagic hypotension,24–27 This is usually caused by severe obstetrical hemorrhage. A study described 72 women with preeclampsia and renal failure. Half of them had HELLP syndrome and a third had placental abruption.28,29

**Patients**

This study involved 40 pregnant women with severe preeclampsia and 20 women with normal pregnancy (control group) in the 3rd trimester of gestation attending El-Shatby Maternity University Hospital.

**Methods**

All patients were subjected to thorough history taking with special emphasis on Gestational age (in weeks). History of medical disease (as chronic hypertension, renal disease, blood diseases, diabetes mellitus, thyroid disorders, liver diseases, cerebrovascular or any neurological abnormality) and Clinical examination regarding Blood pressure and Body mass index. Obstetrical abdominal ultrasound was done by Medison SONOACE X8 live 3D/4D for Gestational age (BPD, AC, FL), Amniotic fluid, Viability and Doppler indices (RI, PI): of both umbilical, middle cerebral artery and uterine arteries. Routine investigations as Fasting blood sugar, Liver enzymes, complete blood count, urine analysis, serum urea, Uric acid, Creatinine and Estimation of serum cystatin were done.30,31 (Tables 1–6).
Table 1 Comparison between the two studied groups according to renal function.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 40)</th>
<th>Control (n = 20)</th>
<th>Test of sig.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min.—Max.</td>
<td>0.30—3.0</td>
<td>0.30—0.80</td>
<td>Z = 3.219∗</td>
<td>0.001∗</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.55 ± 0.89</td>
<td>0.66 ± 0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.85</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min.—Max.</td>
<td>2.0—3.40</td>
<td>3.50—4.80</td>
<td>t = 17.213∗</td>
<td>&lt;0.001∗</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.47 ± 0.29</td>
<td>3.99 ± 0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.50</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min.—Max.</td>
<td>16.0—26.0</td>
<td>15.0—24.0</td>
<td>t = 0.244</td>
<td>0.808</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>21.05 ± 3.19</td>
<td>20.85 ± 2.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>21.0</td>
<td>21.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min.—Max.</td>
<td>3.0—8.20</td>
<td>2.60—4.50</td>
<td>t = 12.596∗</td>
<td>&lt;0.001∗</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>6.76 ± 1.06</td>
<td>3.55 ± 0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7.10</td>
<td>3.50</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*t: Student t-test.  
∗ Statistically significant at p ≤ 0.05.

Table 2 Comparison between the two studied groups according to cystatin.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 40)</th>
<th>Control (n = 20)</th>
<th>T</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystatin (mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min.—Max.</td>
<td>0.53—1.62</td>
<td>0.60—0.81</td>
<td>5.913∗</td>
<td>&lt;0.001∗</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.98 ± 0.29</td>
<td>0.70 ± 0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>0.97</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*t: Student t-test.  
∗ Statistically significant at p ≤ 0.05.

Discussion

Literature would indicate that serum creatinine is a reliable marker of kidney function in pregnancy according to Yang et al. and Stevens et al.25,26,30,34 Serum uric acid levels decrease in first trimester and then increase during pregnancy, with the levels in the third trimester being significantly higher compared to the levels of non-pregnant women.28 Hyperuricemia is often associated with preeclampsia.26 Although it is not found in all women with preeclampsia it often precedes hypertension and proteinuria,32 and may be a risk factor for the progression of renal impairment.13 In our study serum uric acid was found to be above the reference range with significant difference between the mean values for the two groups. Similar results were reported in study by Yang et al.,13 who found significant differences between preeclampsia and controls group. Hyperuricemia in preeclampsia is mainly because of the results of decreased GFR and increased tubular reabsorption, but it may also occur due to amplified placental production of uric acid caused by an increased breakdown of purines in placenta, acidosis, or an increase in the activity of xanthine oxidase/dehydrogenase, thus being not only a marker of pathological state and renal dysfunction but also playing a role in PE pathogenesis.34–36

Table 3 Comparison between the two studied groups according to IUGR and AFI.

<table>
<thead>
<tr>
<th></th>
<th>Study group (n = 40)</th>
<th>Control (n = 20)</th>
<th>Test of sig.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>IUGR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30</td>
<td>75.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min.—Max.</td>
<td>3.5—9.0</td>
<td>5.0—11.0</td>
<td>t = 2.177∗</td>
<td>0.034∗</td>
</tr>
<tr>
<td>5.5 ± 1.40</td>
<td>7.35 ± 1.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>7.50</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

χ²: value of Chi square. MC: Monte Carlo test.  
t: Student t-test.  
∗ Statistically significant at p ≤ 0.05.
Table 4 Comparison between the two studied groups according to umbilical artery Doppler in each gestational age group.

<table>
<thead>
<tr>
<th>UMB</th>
<th>Gestational age (28–32)</th>
<th></th>
<th>Gestational age (32–36)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study group (n = 14)</td>
<td>Control (n = 7)</td>
<td>Study group (n = 26)</td>
<td>Control (n = 13)</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min.—Max.</td>
<td>0.89–1.89</td>
<td>0.91–0.99</td>
<td>0.82–1.90</td>
<td>0.90–1.01</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>1.13 ± 0.24</td>
<td>0.95 ± 0.03</td>
<td>1.07 ± 0.21</td>
<td>0.97 ± 0.03</td>
</tr>
<tr>
<td>Median</td>
<td>1.06</td>
<td>0.97</td>
<td>1.0</td>
<td>0.98</td>
</tr>
<tr>
<td>Z (p)</td>
<td>2.691* (0.007)</td>
<td></td>
<td>1.984* (0.047)</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min.—Max.</td>
<td>0.54–0.70</td>
<td>0.54–0.68</td>
<td>0.50–0.83</td>
<td>0.50–0.68</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.61 ± 0.06</td>
<td>0.58 ± 0.05</td>
<td>0.64 ± 0.09</td>
<td>0.58 ± 0.05</td>
</tr>
<tr>
<td>Median</td>
<td>0.59</td>
<td>0.57</td>
<td>0.63</td>
<td>0.58</td>
</tr>
<tr>
<td>Z (p)</td>
<td>1.245 (0.213)</td>
<td></td>
<td>1.895 (0.058)</td>
<td></td>
</tr>
</tbody>
</table>

Z; Z for Mann–Whitney test.
*Statistically significant at p ≤ 0.05.

Table 5 Comparison between the two studied groups according to uterine artery Doppler in each gestational age group.

<table>
<thead>
<tr>
<th>Uterine</th>
<th>Gestational age (28–32)</th>
<th></th>
<th>Gestational age (32–36)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study group (n = 14)</td>
<td>Control (n = 7)</td>
<td>Study group (n = 26)</td>
<td>Control (n = 13)</td>
</tr>
<tr>
<td>PI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min.—Max.</td>
<td>0.69–1.40</td>
<td>0.66–0.88</td>
<td>0.68–1.10</td>
<td>0.66–0.88</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.90 ± 0.21</td>
<td>0.79 ± 0.08</td>
<td>0.85 ± 0.10</td>
<td>0.75 ± 0.07</td>
</tr>
<tr>
<td>Median</td>
<td>0.87</td>
<td>0.82</td>
<td>0.87</td>
<td>0.70</td>
</tr>
<tr>
<td>t (p)</td>
<td>1.286 (0.214)</td>
<td></td>
<td>3.321* (0.002)</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Min.—Max.</td>
<td>0.38–0.77</td>
<td>0.38–0.50</td>
<td>0.37–0.80</td>
<td>0.36–0.50</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.53 ± 0.14</td>
<td>0.47 ± 0.04</td>
<td>0.51 ± 0.10</td>
<td>0.44 ± 0.06</td>
</tr>
<tr>
<td>Median</td>
<td>0.48</td>
<td>0.49</td>
<td>0.49</td>
<td>0.42</td>
</tr>
<tr>
<td>t (p)</td>
<td>1.539 (0.142)</td>
<td></td>
<td>2.255* (0.030)</td>
<td></td>
</tr>
</tbody>
</table>

t; Student t-test.
*Statistically significant at p ≤ 0.05.

Serum cystatin C is glomerular filtration rate marker that performs better diagnostically than creatinine. Its main advantage is that it is less dependent on body composition than creatinine. Cystatin C level is stable until the third trimester of pregnancy and without significant differences when compared to the levels in healthy non-pregnant women. In the third trimester the level rises, which can be either a consequence of a reduction in glomerular filtration of molecules with physicochemical properties similar of cystatin C (due to changes in the negative charges of the glomerular barrier), or an increase in the synthesis of cystatin.30 In preeclampsia, the serum concentration of cystatin C relates significantly to structural and functional changes in the kidneys.27 Our study results have shown that serum cystatin C levels in PE patients were significantly higher when compared to control group (p = 0.001). Similar results have been demonstrated in other studies.29,30,34 Kristensin et al. showed that that placental production of cystatin C significantly influences serum levels of cystatin C in pregnant women with pre-eclampsia, and also that cystatin C may have a role in the pathogenesis of preeclampsia due to cathepsin (cysteine protease) cystatin C (cysteine protease inhibitor) imbalance in the first trimester.26 Cathepsin is necessary for an undisturbed trophoblast invasion into decidua.37 Yang et al. also indicated that increase in cystatin C levels is associated with disease severity.33 In our study the sensitivity of cystatin was 72.5% in cases of preeclampsia, in contrast to the results of the study by Strevens et al.25 In which the ROC analysis of data showed that serum cystatin C has superior diagnostic accuracy for PE than creatinine and serum uric acid, our ROC analysis showed that serum cystatin C and serum uric acid do have a similar diagnostic accuracy for PE. In our study the sensitivity of Uric acid is 97.5%, while creatinine sensitivity in detection of PE was 60%, so uric acid has more predictive value and diagnostic accuracy for PE when compared to creatinine.

In preeclampsia, the serum concentration of cystatin C relates significantly to structural and functional changes in the kidneys.37 Although studies show that uric acid is one of biochemical parameters that correlates the best with pathological changes in kidneys in preeclampsia,35 Strevens et al.33 Found that the glomerular volume in preeclampsia patients correlated significantly with serum cystatin C level, but less so than with uric acid and creatinine. However, preeclampsia is defined as hypertension with proteinuria the diagnosis of the true condition is still elusive, as pregnant

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women can present with hypertension and proteinuria due to other condition like systemic lupus, our study showed that there was significant difference between study group and control group in proteinuria. Serum cystatin reflecting GFR, is an indicator of a different feature of the disease and could thereby be helpful in the diagnosis of pure preeclampsia and possibly also indicate severity of the disease. In agreement with our study Bibi Shahnaz Aali et al.\textsuperscript{35} in their study found that umbilical artery mean pulsatility index was significantly higher in preeclampsia than control group, in our study patients with severe preeclampsia showed significantly higher values of PI than control group with a mean (1.13 ± 0.24), (1.07 ± 0.21) at gestational age 25–31 and 32–36, respectively. Also we found that in our study uterine artery Doppler in normal pregnancy compared to severe preeclamptic patient; showed that PI and resistance index of study group significantly higher at gestational age\textsuperscript{32–36} with a mean (0.85 ± 0.10), (0.51 ± 0.10), respectively. Gerad Albaiges et al.,\textsuperscript{36} conducted a study on Doppler assessment of uterine arteries in pregnancy found that cases with severe preeclampsia had high mean pulsatility index than normal pregnant, while Mulidhar (166) result study found the RI of uterine significantly higher in severe preeclampsia between 24–28 and 32–36. In our study the Doppler of middle cerebral artery showed that; there were significant differences in pulsatility index and resistance index between study group and control group with a mean of PI (1.29 ± 0.17) and RI (0.76 ± 0.06) at gestational age 25–31, while the mean of PI (1.25 ± 0.09) and RI (0.73 ± 0.08) between 32 and 36 weeks. In disagreement with our study Dubiel et al.\textsuperscript{38} reported that there is no significant difference between preeclampsia and normal pregnancy regarding middle cerebral artery Doppler, the discrepancy in the findings between their study and ours may be explained by the greater sample size, non-selection of the cases and different gestational age of patient. Patients with severe preeclampsia can defined on the basis of the level of proteinuria >5 g. Display a rise in cystatin levels which could support a possible clinical use in this way. The gold standard of diagnosis is still considered to be a renal biopsy showing endotheliosis,\textsuperscript{39–48} and future studies will have to confirm the association of cystatin level with the true condition as well as the GFR in pregnancy and preeclampsia. So, serum cystatin C can replace renal biopsy which is an invasive technique.

**Conclusion**

Cystatin c serum levels may have significant role as a marker of preeclampsia and alternative marker of renal function in preeclampsia, even more so when used in combination with uric acid levels which is still the most accurate predictor of preeclampsia and most accurate indicator of renal function of preeclampsia.

**Conflict of interest**

The authors have nothing to disclose and declare no conflict of interest, whether personal or financial.

**Ethical approval**

Written informed consent was obtained from the patients for publication of this case report and accompanying images.

**Ethical disclosures**

**Protection of human and animal subjects**

The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data**

The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent**

The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.
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