Use of the Urinary Protein/Urinary Creatinine Index in Patients with Preeclampsia

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ABSTRACT

Preeclampsia is the main cause of maternal morbidity and mortality in Mexico, accounting for up to 34% of all maternal deaths. Current evidence refers to the usefulness of the protein/creatinine ratio as a predictor of preeclampsia, and its outcome is comparable with the determination of 24-hour proteinuria. To determine the usefulness of the protein/creatinine index in an isolated urine sample in patients with preeclampsia. A series of cases of pregnant women diagnosed with preeclampsia was employed in which the protein/creatinine index was calculated in an isolated sample of urine in order to describe the results, associating this index with the evolution of the patients in terms of maternal outcomes. Statistical analysis was performed in the SPSS ver. 20 statistical software program, evaluating the correlation between urinary protein/urinary creatinine ratio and the 24-h determination of urinary proteins, performing the Pearson correlation coefficient, with the determination of significant proteinuria >300 mg/dL in 24-h urine as gold standard. A protein/creatinine ratio equal to or greater than 0.3 mg/dL, obtained from an isolated urine sample, was considered as a proteinuria equal to or greater than ≥300 mg/dL in the analysis of 24-h urine. The protein/creatinine ratio could be used for rapid and reliable protein detection in patients with a presumptive diagnosis of preeclampsia.
INTRODUCTION

Hypertensive disorders of pregnancy complicate up to 10% of all pregnancies, representing high morbidity and maternal and perinatal mortality \[^1\]. Preeclampsia, whose definitive cause is still unknown, belongs to the spectrum of hypertensive disorders of pregnancy and, if not diagnosed and/or treated properly, leads to fatal consequences for mother and baby \[^2\]. Every day, worldwide, approximately 800 women die from preventable causes in pregnancy, childbirth, and puerperium; 99% of these deaths occur in low-income countries \[^3\]. Moreover, preeclampsia is the second leading cause of maternal death worldwide, each year, almost 300,000 lose their life in this process and over 500,000 babies die as a consequence of preeclampsia \[^4\].

Early diagnosis of preeclampsia is important to ensure maternal-fetal well-being. Delay in diagnosis, adequate primary care, and referral to the second level for specialist assessment are important contributors to adverse maternal and fetal outcomes \[^5\].

The diagnosis of preeclampsia is performed with the presence of arterial hypertension: >140/90 mmHg after 20 weeks of gestation. Formerly, it was mandatory the presence of significant proteinuria, that is, during pregnancy, delivery, and puerperium, with: quantification of proteins in a collection of 24-h urine 24 h≥300 mg/dL; urine protein/urinary creatinine ratio in a random urine sample ≥0.3, and the presence of 1+ on a test strip (labstick) in a sample taken at random (use only if quantitative methods are not available) \[^5, 6\]. The novel guidelines consider the diagnosis of preeclampsia when a woman after 20 weeks identifies arterial hypertension and clinical and laboratory severity criteria even when significant proteinuria is not demonstrated during the initial approach \[^7\].

In rare cases, preeclampsia may present with proteinuria and hypertension prior to 20 weeks of gestation, when this is usually associated with predisposing factors such as hydatidiform mole, multiple pregnancy, fetal hydrops, chronic renal injury, or the antiphospholipid antibody syndrome \[^8\]. Unfortunately, the disease is progressive, the evolution is unpredictable, and only the interruption of the pregnancy halts its progression \[^9\].

In relation to the urine protein test, a negative test strip does not rule out proteinuria and requires confirmation with quantitative methods. In fact, a negative value or stroke should not be ignored in a pregnant woman with recent hypertension or with symptoms or signs suggestive of preeclampsia; 12% of negative/trace results will be false negative compared with 24-h proteinuria of 300 mg/dL \[^10\]. Several studies have reported a correlation between the collection of 24-h urine with protein determination and urinary protein/urinary creatinine ratio in a randomized dose \[^11-13\].

The implementation of Urinary Protein/Urinary Creatinine Index (PI), is an inexpensive and excellent alternative to 24-h urine collection, is useful in the diagnosis of preeclampsia, and can be utilized as an admission test for emergency services in patients for classification of Hypertensive Diseases Of Pregnancy \[^14\]. The recognition, classification, and appropriate management of hypertensive disorders of pregnancy and associated complications can considerably reduce maternal and perinatal deaths \[^15\]. The 24-h urine collection for protein determination in women with suspected preeclampsia may delay the diagnosis of preeclampsia. Another factor involved in not completing urine collection is the interruption of pregnancy. Implementation of the PI has been employed to shorten the time for the diagnosis of preeclampsia \[^16, 17\].

The evaluation of proteinuria plays an important role in the control of pregnant women. The gold standard for determination of significant proteinuria in pregnancy is the confirmation of 300 mg/day in urine collected during 24 hours. On many occasions, analysis of protein determination in 24-hour urine is incomplete and somewhat bothersome for patients. The Theory of Patient Success in Hypertension in Pregnancy and the International Society for the Study of Hypertension in Pregnancy has proposed the use of PI as an alternative in the 24-h urine collection \[^18, 19\].

A systematic review by Cote and colleagues concludes that the PI with a cut-off of 0.265 correlates with proteinuria of 300 mg/day in pregnant women \[^20\]. However, this problem has not, to our knowledge, been studied in pregnant women in the State of Mexico. Therefore, this study was performed to observe the correlation between the PI and 24-h urine collection with protein determination in pregnant women of more than 20 weeks of gestational age (GA), with arterial hypertension.
MATERIALS and METHODS

This was a descriptive and prospective study, registered at the Autonomous University of the State of Mexico (UAEMex) (code EGO(606030)-0416). All pregnant women after 20 weeks GA, with arterial hypertension>140/90 mmHg and admitted to the Emergency Department of the Hospital Materno Infantil ISSEMyM, Toluca, State of Mexico, during the period from January 1, 2015 to December 31, 2015 were included. All recruited women signed informed consent.

Through a non-probabilistic of consecutive cases, the sample size was calculated to carry out inference with a 95% Confidence Level (95% CI) and a 5% CI in a population of approximately 80 cases of women with preeclampsia during pregnancy and puerperium. Urine samples were taken at random for the determination of urinary Protein/urinary Creatinine Index (Pl) on admission to the Emergency Department, and a 24-h urine collection was performed.

A 20-mL urine specimen was collected in a sterile bottle at the time of admission to the Emergency Department and sent to the laboratory for protein and creatinine determination. Urine was collected during 24 h in a container. Protein determination was performed by the Kjeldahl method for its speed, accuracy, and reproducibility of results. The Pl was obtained by dividing the urinary protein concentration (mg/dL) by the urinary creatinine concentration (mg/dL) of the random sample: PI = Pu/CrU.

Statistical analysis was performed with the SPSS ver. 20 statistical software program, evaluating the Pearson correlation coefficient between the urinary protein/urinary creatinine ratio and determination of urinary proteins in 24 h.

RESULTS

A total of 73 cases were obtained based on the selection criteria. It was possible to identify that of the patients with preeclampsia in our study, 53 (72.6%) corresponded to 18–35-years-of-age group, and 20 (27.3%), patients aged >35 years. The group of first-gestation patients (26 women) represented 35.6% of the total patients included, followed by the second-gestation group (25 women) with 34.2%, and third, the group of patients with three or more pregnancies (22 women), 30.1%.

Gestational age ranged from 20–26 weeks, representing 4.1% (3 patients), with 10.9% of these from the puerperium group (8 patients) and 24.6% from the 27–33-week gestational group (18 patients), while 60.2% represented the group with 34–41 weeks of gestation (44 patients). Of the total number of patients, 75% (55 women) had only preeclampsia, and 25% (18 women) had some comorbidities as follows: renal failure in 5.4%; chronic hypertension in 5.4%; infection (one case of pneumonia and one case of renal absscess) in 2.7%, gestational diabetes in 2.7%, and pregestational diabetes in 1.3%, including twin pregnancy in 6.8%. With regard to the complications of preeclampsia, 61.6% had no complications, 30% developed preeclampsia with severity data, and the HELLP syndrome (haemolysis, elevated liver enzymes and low platelets) was present in 5.4%, followed by placenta abruption in 1.3%, as well as obstetric hemorrhage.

Proteinuria found in an isolated sample of urine showed an average of 13.35 mg/dL in the group of patients aged 20–26 years. The group with the most significant mean, corresponding to those aged between 27 and 33 weeks of gestation, showed a mean of 322.45 mg (Table 1).

<table>
<thead>
<tr>
<th>Weeks of gestation</th>
<th>Lowest value (mg/dL)</th>
<th>Highest value (mg/dL)</th>
<th>Mean (mg/dL)</th>
</tr>
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<tr>
<td>20-26</td>
<td>12</td>
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<td>3700</td>
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<td>34-41</td>
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<td>2520</td>
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<td>Puerperium</td>
<td>5.6</td>
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Table 1. Proteinuria by weeks of gestation or puerperium
In general, a PI equal to or greater than 0.3 mg/dL, obtained from an isolated urine sample, was considered as a proteinuria equal to or greater than ≥300 mg/dL in the analysis of 24-h urine (Table 2). Given the full data, the Pearson correlation between both parameters was low (0.04), but by deleting the three outliers, those with PI higher than 20, then the correlation was of 0.64.

<table>
<thead>
<tr>
<th>PI</th>
<th>Proteinuria in 24 h urine (mg/dL)</th>
<th>PI</th>
<th>Proteinuria in 24 h urine (mg/dL)</th>
<th>PI</th>
<th>Proteinuria in 24 h urine (mg/dL)</th>
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<td>0.57</td>
<td>496.8</td>
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</tbody>
</table>

It was possible to identify the lowest value of creatinine in isolated mist of urine in the 27–33 weeks-of-gestation group with a value of 6.8 mg/dL with a mean of 50.92 mg/dL. We also identified that the group with 34–41 weeks of gestation had the highest creatinine value with 183.4 mg/dL, with an average of 51.09 mg/dL (Table 3).
**Table 3. Mean creatinine by weeks of pregnancy and puerperium**

<table>
<thead>
<tr>
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<tr>
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<td>165.8</td>
<td>50.92</td>
</tr>
<tr>
<td>34-41</td>
<td>9.9</td>
<td>183.4</td>
<td>51.09</td>
</tr>
</tbody>
</table>

**DISCUSSION**

Eslamian et al. (2011) found a strong correlation between urine protein creatinine ratio and protein index at 24 h ($r = 0.77; \ p = 0.001$), with a significant ($p < 0.001$) Receiver Operating Characteristic (ROC) curve for proteinuria $>300 \text{ mg/dL}$ of 0.926 (95% CI: 0.85–0.99), Cut-off point (PI): 0.22 mg/dL, with 87.9% sensitivity, 92.6% specificity, a Positive Predictive Value (PPV) of 90.6%, and a Negative Predictive Value of 89.3%[^14]. In our work we did not perform ROC curves.

A Systematic review in 2012 included 2,978 women in whom the diagnostic value was evaluated using the urine protein creatinine ratio in a random urine sample, with 65–89% sensitivity and 3–87% specificity. However, a result of urine protein creatinine ratio between 0.30 and 0.35 optimizes, to a certain degree, combining sensitivity and specificity of >80%. For example, specificity and sensitivity were 85% 95% (95% CI: 0.78–0.91) and 76% 95% (95% CI: 0.73–0.78) for a cut-off point of 30 mg/mmol/urinary creatinine and among women with hypertension in pregnancy, respectively[^21]. This value is similar to our PI cut off proposal of 0.3.

Another study carried out by Kayatas in 2013 in Turkey identified a total of 127 patients, among whom 63.5% had protein in the urine of 24 h >300 mg; of these patients, 94 obtained a range of 300–2,000 mg/dL and 33 had >2,000 mg/dL. When analyzing the ROC curve, the urine protein creatinine ratio correlation with a cut-off point of 0.28 was ideal for detecting proteinuria >300 mg, with a sensitivity of 60.4% and a specificity of 77.9%. PPV and NPV were 77.5 and 60.9%, respectively. A PI cut-off point of 0.19 could exclude preeclampsia with 100% sensitivity. ROC curve for proteins between 300 and 2,000 mg/day in 24-h urine was 0.74 (95% CI: 0.66–0.80) and 0.99 (95% CI: 0.95–0.99) [^22].

A study conducted in Iran by Mohseni in 2013 found a correlation between the urine protein creatinine ratio, and 24-h urine collection, with a Pearson correlation of 0.502 with a sensitivity and specificity of 87.5 and 84.2%, respectively[^23]. Our Person correlation (deleting the three outliers) is similar to this value.

Another study conducted in Korea in 2013 comprises a retrospective analysis of a registry of 140 pregnant women admitted to the hospital with suspected preeclampsia from January 2006 to June 2011 with protein in urine and random 24-h urine collection were assessed for protein levels in urine and its correlation with the urinary protein/creatinine ratio. The two tests were performed in 79 (85%) patients with significant proteinuria, i.e. 300 mg/24 h. Six cases had values of >5,000 mg/24 h, corresponding to a diagnosis of severe preeclampsia, finding a high correlation between the urinary protein/creatinine ratio and 24-h urine collection, with $r = 0.823, p < 0.01$, with a cut-off point of 0.63 and 4.68 for 300 mg/24 h and 5,000 mg/24 h of protein excretion, respectively, with sensitivity, specificity, and PPV and NPP of 87.1, 100%, 100, and 58.3, 85, 50, and 100% for significant and severe preeclampsia, respectively [^24].
CONCLUSION

Protein determination in urine is mandatory for establishing the diagnosis of preeclampsia. This protein measurement is carried out in a collection of urine for 24 h and comprises the gold standard for quantitative determination.

Defining significant proteinuria as the quantification of 300 mg/day, urine collection is cumbersome and requires time for its determination. Studies have shown inadequate urine collection in up to 37% of samples. Waiting for protein quantification results in 24-h urine may delay the diagnosis and management of the patient with preeclampsia. Thus, a fast and accurate test can provide ambulatory services and efficient monitoring of proteinuria and can shorten the length of hospitalization. Alternatives such as urine test strips and the urinary protein/urinary creatinine index have been considered for the diagnosis of proteinuria.

The urine protein creatinine ratio could be employed for rapid and reliable protein detection in patients with a presumptive diagnosis of preeclampsia.

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REFERENCES


