Use of a random urinary protein-to-creatinine ratio for the diagnosis of significant proteinuria during pregnancy

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OBJECTIVE: The purpose of this study was to evaluate whether a random urinary protein-to-creatinine ratio is a clinically useful predictor of significant proteinuria (300 mg/24 hour).

STUDY DESIGN: The medical records of 138 women who completed both a random urinary protein-to-creatinine ratio and a 24-hour urine collection for the evaluation of preeclampsia were reviewed. Urine samples for the random protein-to-creatinine ratio were collected before the 24-hour urine collection. With the use of a protein level of at least 300 mg in the 24-hour urine sample as the gold standard, the sensitivity and specificity of the random protein-to-creatinine ratio for the diagnosis of significant proteinuria were determined with a range of cutoffs.

RESULTS: Fifty percent of the study population had significant proteinuria. The data suggest that a cutoff below 0.14 ruled out significant proteinuria. The best cutoff of ≥0.19 yields a sensitivity of 90% and a specificity of 70%. All of the false-negative test results had 24-hour urine protein levels below 400 mg; 13 of the 21 false-positive results had levels that ranged from 250 to 300 mg.

CONCLUSION: The random urinary protein-to-creatinine ratio is strongly associated with the 24-hour total protein excretion. A level below 0.14 can rule out significant proteinuria. A best cutoff of ≥0.19 is a good predictor of significant proteinuria. With further study, the random urinary protein-to-creatinine ratio could replace the 24-hour urine collection as a simpler, faster, more useful method for the diagnosis of significant proteinuria. (Am J Obstet Gynecol 2001;185:808-11.)

Key words: Random urinary protein-to-creatinine ratio, significant proteinuria, sensitivity, analysis, ROC curve

The 24-hour urine collection has been the gold standard for making the diagnosis of significant proteinuria in patients with pregnancy-induced hypertension.1,2 The test is cumbersome and takes 24 hours to complete, which leads to delay in diagnosis and inaccurate results as the result of incomplete collections. Noncompliant patients are often admitted to the hospital to ensure a proper collection. In addition, for patients who are diagnosed with hypertension while in labor, the clinician is unable to complete a 24-hour collection. A rapid method for diagnosing significant proteinuria could help clinicians make more timely decisions regarding delivery and the use of magnesium for seizure prophylaxis. The dipstick has been shown to be inaccurate with 1 study that shows that 66% of the patients with negative or trace protein had significant proteinuria when the sample was compared with the 24-hour urine collection.4

Many studies in nonpregnant women have shown that the random urinary protein-to-creatinine ratio can be used to quantify the degree of proteinuria with good accuracy,5,6 with a level greater than or equal to 0.20 considered evidence of significant proteinuria.7,8 Despite several studies that showed a strong linear association between the random urinary protein-to-creatinine ratio and the 24-hour total protein excretion in pregnant women,9-14 the only study that examined its usefulness as a screening test suggested that no single cutoff could adequately distinguish the presence of significant proteinuria.3 The current study was designed to evaluate the usefulness of a random urinary protein-to-creatinine ratio collected before a 24-hour urine collection for the diagnosis of significant proteinuria in a larger sample population.

Material and methods

The medical records of 138 women who completed both a random urinary protein-to-creatinine ratio and a 24-hour urine collection for the evaluation of significant proteinuria were reviewed. Significant proteinuria was defined as ≥300 mg protein in a 24-hour urine collection. All random samples were collected before the 24-hour urine collection. None of the samples were first voided.
morning urine. Patients with pre-existing intrinsic renal disease were excluded. No patients in the study group had a coexisting urinary tract infection. The urinary protein concentration was determined with the use of the Dimension (Dade Behning, Inc, Newark, Del) clinical chemistry system UCFP method, which uses the pyrogalol red-molybdate method; the urinary creatinine test was performed with the use of the Dimension (Dade Behning) clinical chemistry system CREA method, which uses a modified Jaffe reaction. Although the results could be accessed by the clinicians, no clinical decision was based on the random urine protein-to-creatinine ratio during the study period. The study was approved by the Brigham and Women’s Hospital Human Research Committee.

Statistical analyses were performed with the STATA (STATA Corp, College Park, Texas) statistical package. The linear association between the random urinary protein-to-creatinine ratio and the 24-hour total protein excretion was evaluated by generating a least-squares regression line. The Pearson correlation coefficient ($r$) was determined from the calculated coefficient of determination ($R^2$). With the use of the results of the 24-hour urine collection as the gold standard, the sensitivity and specificity of the random urinary protein-to-creatinine ratio for significant proteinuria were determined with a range of cutoffs. A receiver operator characteristic (ROC) curve was then constructed, and the area under the curve was calculated.

**Results**

A total of 138 women completed both a random urinary protein-to-creatinine ratio and a 24-hour urine collection during the study period. The median age of the study population was 30 years (range, 16-49 years). Eighty-four percent of the patients whose statistics were studied were in the third trimester compared with only 0.7% and 15.2% in the first and second trimesters, respectively. Fifty-two percent of the women who were studied were nulliparous. Pregestational hypertension and diabetes were found in 10% and 3% of the study population, respectively.

Fifty percent of the study population ($n = 69$) had significant proteinuria as determined by the 24-hour urine collection. The random urinary protein-to-creatinine ratio was highly correlated with the 24-hour total protein excretion, with a correlation coefficient of 0.80 ($P < .001$; Fig 1).

The ROC curve for the random urinary protein-to-creatinine ratio is shown in Fig 2. The area under the ROC curve is 0.91 (95% confidence interval, 0.87 and 0.96). The sensitivity, specificity, positive predictive value, and negative predictive value for various cutoffs are shown in the Table. The cutoff of $0.19$ yields a sensitivity of 90% and a specificity of 70%. With the use of this cutoff, there were 7 false-negative test results and 21 false-positive test results. Fig 3 shows that most of the false-negative test results and false-positive test results were within 50 mg of the cutoff of 300 mg that was used for the diagnosis of significant proteinuria with a 24-hour urine sample. None of the false-negative test results had more than 380 mg protein on the 24-hour urine collection, with 5 of the 7 test results having levels between 300 and 340 mg. Thirteen of the 21 false-positive test results (62%) had levels between 250 and 300 mg of protein for the 24-hour urine collection.

**Comment**

Preeclampsia is often distinguished from gestational hypertension by the presence of significant proteinuria. The gold standard test for the diagnosis of significant proteinuria remains the 24-hour urine collection. However, it is cumbersome and time-consuming. Although it is considered the gold standard, it can be inaccurate because of an incomplete collection. Simpler methods (such as the urinary dipstick and the random protein-to-creatinine ratio) have been criticized because they measure the...
urinary protein concentration only at 1 point in time. Because protein excretion has been shown to vary over the course of the day and with positional changes, a single measurement may not accurately reflect the 24-hour total protein excretion. In the setting of preeclampsia, which is marked by renal vasospasm, this variation may be more marked. The urinary dipstick appears to be a poor predictor of significant proteinuria for the evaluation of preeclampsia, with 1 series showing that two thirds of the samples with negative or trace protein by dipstick had significant proteinuria. On the other hand, the urinary protein-to-creatinine ratio has been shown to be highly correlated with the 24-hour total protein excretion in both normotensive and hypertensive pregnant women. This relationship has also been demonstrated in pregnant patients with diabetes mellitus. Correlation coefficients reported range as high as 0.928 to 0.995, and the degree of correlation did not vary by trimester of pregnancy during which the sampling occurred. Despite the high degree of linear correlation, a best cutoff has not been described for pregnancy, and the test is not widely used during pregnancy. To date, only 1 study has evaluated the ROC curve for the random urinary protein-to-creatinine ratio as a predictor of proteinuria during pregnancy. Although there was a strong linear association, the ROC curve did not reveal a reliable cutoff. However, their sample size was limited (n = 42). In addition, a number of their samples were collected after the 24-hour urine collection, which could alter the results if the patients remain at bedrest during the collection period. We chose to evaluate the usefulness of the random urinary protein-to-creatinine ratio that was collected before the 24-hour urine because it most closely resembles how the test would be used in practice. Our study revealed that the random urinary protein-to-creatinine ratio is an outstanding test for discriminating between insignificant and significant proteinuria, as demonstrated by an area under the ROC curve of 0.914.

In determining what we considered to be the best cutoff, we believed that it was important to maximize sensitivity, given the potential consequences of missing the diagnosis of preeclampsia. A cutoff below 0.14 ruled out significant proteinuria; however, the specificity was only 51%. To maximize the specificity while maintaining a sensitivity of 290%, we set our criterion of positivity as ≥0.19. This yielded a sensitivity of 90% and a specificity of 70%. The negative predictive value was 87% in our population (in which the prevalence of significant proteinuria was 50%). Most of the false-negative test results and false-positive test results were within 50 mg of the cutoff of 300 mg for a 24-hour urine, thus the random urinary protein-to-creatinine ratio was in very close agreement with the 24-hour urine. The main concern with the discordant values is the false-negative test results because real cases may be missed; these are not likely to be due to collection errors with the 24-hour urine sample. However, all of the false-negative test results had only borderline-to-mild proteinuria, with 5 of 7 results having levels between 300 and 350 mg protein. No patients with proteinuria over 380 mg protein were missed. It is unclear whether these false-negative results would impact significantly the clinical course of the patient, given the mildness of their disease.

Of the false-positive results, it is unclear how many of these may actually represent true-positive results because the total protein excretion as measured by the 24-hour urine collection is more susceptible to underestimation than overestimation because of incomplete collection. Comparing the results of the urinary protein-to-creatinine ratio with a 24-hour urine collection obtained with a Foley catheter would be a more valid method for the evaluation of this issue and should be considered for future study.

We were unable to assess the usefulness of the random urine protein-to-creatinine ratio for the diagnosis of severe proteinuria in our dataset because there was only 1

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Fig 3. Performance of the random urinary protein-to-creatinine ratio for the detection of significant proteinuria with the use of a best cutoff of 0.19. The open triangles represent outliers that are depicted but not plotted to scale. All of the outliers were true positives.
patient with proteinuria above 5 g on the 24-hour urine collection. Although a larger study would yield more patients with severe proteinuria, it would be difficult to enroll an adequate number of cases for analysis, given the low prevalence of severe proteinuria. A previous study conducted in nonpregnant subjects revealed that the accuracy of the random urinary protein-to-creatinine ratio was independent of the degree of proteinuria, which suggests that the test can be used to identify patients with severe-range proteinuria.\(^6\) Although some studies have reported a greater variability for proteinuria above 1 g (which suggests lower correlation),\(^6,9,11,14\) the few studies that have evaluated the ability of the test to discriminate between patients with and without severe proteinuria suggest that the test performs very well with a reported sensitivity of 100%.\(^6,9,14\) In other words, all of the patients with severe proteinuria would have been identified as having severely elevated protein-to-creatinine ratios.

It is important to remember that the interpretation of any diagnostic test is influenced by the clinical suspicion or pretest probability and the prevalence of the disease in the population under study. For patients with a high pretest probability of disease and a negative random urinary protein-to-creatinine ratio, repeating the test or proceeding with collection of a 24-hour urine is a reasonable option. Repeating a random sample is much easier and quicker to accomplish. In our institution, the turnaround time is 1 hour if the test is ordered immediately and 4 to 6 hours if the test is ordered as a routine study. Furthermore, the positive and negative predictive values may be different in other populations, depending on the prevalence of significant proteinuria.

Similar to our study, the random protein-to-creatinine ratio has been previously shown to be strongly associated with the 24-hour total protein excretion during pregnancy.\(^3\)\(^-\)\(^12\) However, our study expands the previous observations by analyzing the ROC curve to evaluate whether a best cutoff can be used to accurately diagnose significant proteinuria. Our larger study suggests that the random protein-to-creatinine ratio is a good alternative to the 24-hour urine collection for the diagnosis of significant proteinuria. Future efforts should be aimed at the correlation of the random urinary protein-to-creatinine ratio to the pretest probability of true disease. In addition, the clinical outcome and cost-effectiveness of a treatment schema that uses a random urinary protein-to-creatinine ratio for the diagnosis of significant proteinuria should be prospectively evaluated.

**REFERENCES**