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CLINICAL ARTICLE

Predictive value of 4-, 8-, and 12-h protein and protein-to-creatinine ratio for detection of pre-eclampsia

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ABSTRACT

Objective: To evaluate the accuracy of protein measurement and protein-to-creatinine ratio (PCR) in 4-, 8-, and 12-h urine samples as compared with 24-h urine samples as the gold standard method for suspected pre-eclampsia. *Methods:* In a prospective study, 120 women at more than 20 weeks or pregnancy with high blood pressure and no history of hypertension were enrolled between April 2010 and December 2012. Net protein excretion and PCR were evaluated in urine samples collected over 4 h, 8 h, 12 h (day), and 12 h (night) and compared with 24-h protein excretion as the gold standard test. *Results:* A significant positive correlation was found between the values of the 4-h, 8-h, 12-h (day), and 12-h (night) samples and the 24-h samples. The best cutoff point of the PCR to detect significant urine protein excretion was 0.28, 0.24, 0.25, and 0.23 for the 4-h, 8-h, 12-h (day), and 12-h (night) samples, respectively. *Conclusion:* Measurement of protein and PCR in 4-h, 8-h, and 12-h urine samples might provide an alternative test for detecting proteinuria among pregnant women with suspected pre-eclampsia when there is insufficient time to collect 24-h urine samples.

1. Introduction

Hypertensive disorders complicate 5%–10% of all pregnancies (Box 1) and, together with hemorrhage and infection, contribute greatly to maternal morbidity and mortality. Hypertension is diagnosed empirically when appropriately taken systolic or diastolic blood pressure exceeds 140 or 90 mmHg, respectively [2].

Pre-eclampsia is a pregnancy-specific syndrome that can affect almost every organ. Although it is much more than simple gestational hypertension with proteinuria, the appearance of proteinuria remains an important diagnostic criterion (Box 2). As an objective marker, proteinuria reflects a system-wide endothelial leak, which characterizes the syndrome of pre-eclampsia [2].

Women with an initial diagnosis of pre-eclampsia should be admitted and assessed in hospital. Maternal blood tests should be done twice a week (and again in response to a change in clinical status) for most women diagnosed with pre-eclampsia, including hemoglobin, platelet count, liver enzymes, electrolytes, creatinine, and uric acid [1].

Abnormal protein excretion is arbitrarily defined as 24-h urinary excretion exceeding 300 mg, a urine protein-to-creatinine ratio (PCR) of more than 0.3, or a persistent PCR of 30 mg/dL in random urine samples [2]. Measurement of 24-h urine protein excretion has been the gold standard for quantifying urinary protein. However, it is an inconvenient and time-consuming test, both for the woman and for the staff collecting the sample [3–5], in a situation when the timely and accurate diagnosis of pre-eclampsia is essential to avoid significant maternal and fetal morbidity and mortality [6].

Shortening the time to diagnosis of pre-eclampsia would provide clinical benefits, such as reducing the time to delivery and enabling earlier use of prenatal glucocorticoids for fetal pulmonary maturity [7]. Furthermore, those women without pre-eclampsia can be discharged earlier [8].

Several methods are available for measuring proteinuria. One of the most commonly used methods is spot PCR measured by a urinary dipstick test owing to its simplicity and low cost. However, dipstick qualitative determinations depend on urinary concentration and are notorious for false-positive and negative results. Determination of urinary PCR may supplant the cumbersome 24-h quantification [2], but its drawbacks include inconsistency, poor correlation with 24-h urine protein excretion [3], and wide fluctuations throughout the day owing to water intake, exercise, diet, posture, or improperly trained laboratory staff [9,10].

In this context, a rapid and accurate diagnostic test with the capability of predicting 24-h urine protein excretion would be valuable. The aim of the present study was therefore to evaluate the accuracy of protein measurement and PCR values in 4-h, 8-h, and 12-h urine samples as compared with a 24-h urine sample as the gold standard method

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Box 1
Classification of hypertensive disorders of pregnancy [1].

- Chronic hypertension
- Gestational hypertension
- Pre-eclampsia, either de novo or superimposed on chronic hypertension
- White coat hypertension

for suspected pre-eclampsia, with the view to introduce a diagnostic test for pre-eclampsia that avoids the inconvenience of 24-h urine collection and protein measurement.

2. Materials and methods

The present prospective study enrolled pregnant women with suspected pre-eclampsia who were referred to the University Hospital of Shahid Akbar-Abadi, Tehran, Iran, between April 1, 2010, and December 31, 2012. The study was approved by the ethics committee of the Iran University of Medical Science, and all participants provided written informed consent.

The study patients were selected using simple random sampling. The inclusion criteria were women with a singleton pregnancy of more than 20 weeks who had a systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg, and no previous history of hypertension or proteinuria. The exclusion criteria were chronic kidney disease, urinary tract infection, chronic hypertension, diabetes, and fetal growth restriction.

All women with an initial diagnosis of hypertension were admitted to the hospital and instructed to have relative bed rest and a regular diet. They were evaluated for signs of severity (including persistent headache, blurred vision, and stomach burn) and tested for liver function, creatinine levels, platelets, and proteinuria.

To evaluate proteinuria, all patients were requested to urinate at 8 am, and then their urine was accumulated in separate bottles from 8 am to 12 pm (B1), 12 pm to 8 pm (B2), and 8 pm to 8 am the next day (B3, night sample). The sample in each bottle was individually evaluated for volume, protein, and creatinine, and the PCR was calculated. Bottles B1 and B2 were then mixed to measure protein and PCR in the first 12 h (day sample). Last, B3 was added to B1 and B2 to measure the volume, protein, and creatinine, and calculate the PCR in 24 h.

Data analysis was performed with SPSS version 16 (SPSS Inc., Chicago, IL, USA). Descriptive data were reported as means ± SD. The relationship between the PCR in the 4-h, 8-h, and 12-h urine samples, and the 24-h urine sample was assessed via the intra-class correlation coefficient. The sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs) of the various urine samples were determined using the 24-h urine sample as the gold standard. The cutoff point for predicting proteinuria was determined from a receiver operating characteristic (ROC) curve. $P < 0.05$ was considered to be statistically significant.

Box 2
Criteria for the diagnosis of pre-eclampsia [1].

- Proteinuria (spot urine protein-to-creatinine >0.3 mg/mg, >300 mg/day, or ≥ 1 g/L)
- Maternal organ dysfunction including renal insufficiency (creatinine >1.02 mg/dL), liver involvement (elevated transaminase at least twice the upper limit of normal, with or without right upper quadrant or epigastric abdominal pain), neurologic symptoms (eclampsia, altered mental status, blindness, stroke, severe headaches, and persistent visual scotomata), hematologic complications (thrombocytopenia, platelet count <150,000 per dL; disseminated intravascular coagulation, and hemolysis)
- Uteroplacental dysfunction, fetal growth restriction

3. Results

Among 120 inpatient hypertensive pregnant women enrolled during the study period, 57 had proteinuria of 300 mg or more in 24 h and were diagnosed with pre-eclampsia. The remaining 63 hypertensive patients did not have proteinuria at levels indicative of pre-eclampsia.

Among the women with pre-eclampsia and those with gestational hypertension, respectively, the mean maternal age was 28.75 ± 6.15 and 28.13 ± 5.57 years; the mean length of pregnancy at admission was 33.32 ± 3.11 and 33.70 ± 3.14 weeks; and 31/57 (60%) and 34/63 (49%) were nulliparous (Table 1).

Mean systolic blood pressure was 152.04 ± 10.77 mmHg and 148.35 ± 6.82 mmHg, and mean diastolic blood pressure was 97.39 ± 8.07 mmHg and 95.33 ± 6.97 mmHg among women with pre-eclampsia and those with gestational hypertension, respectively (Table 1). Mean 24-h urine protein was 421.12 ± 180.97 mg and 122.33 ± 35.9 mg, and mean 24-h PCR was 0.3208 ± 0.058 and 0.096 ± 0.046 among women with pre-eclampsia and those with gestational hypertension, respectively. The mean 4-h, 8-h, 12-h (day), and 12-h (night) urine protein and PCR values are shown in Table 1.

The predictive values of 4-h, 8-h, 12-h (day), and 12-h (night) urine protein and PCR were calculated by ROC curve analysis using 24-h urine protein as the gold standard. Table 2 shows the best cutoff values, together with sensitivity, specificity, PPV, and NPV, for detecting 24-h urinary protein excretion exceeding 300 mg.

The best cutoff point of PCR values was 0.28 for 4-h samples (sensitivity 87.7%; specificity 98.1%; Table 2, Fig. 1A), 0.24 for 8-h samples (sensitivity 94.7%; specificity 95.2%,; Table 2, Fig. 1B), 0.23 for 12-h (night) samples (sensitivity 94.7%; specificity 96.8%; Table 2, Fig. 1C,), and 0.25 for 12-h (day) samples (sensitivity 96.8%; specificity 98.4%; Table 2, Fig. 1D). Similarly, the best cutoff points of net protein values were 58, 96, 134, and 146 mg for the 4-h, 8-h, 12-h (night), and 12-h (day) samples respectively (Table 2).

Urine protein and PCR for the 4-h, 8-h, 12-h (day), and 12-h (night) samples correlated well with the 24-h sample (Tables 3 and 4). There was a significant positive correlation among the 4-h, 8-h, 12-h (day),

Table 1
Characteristics of the study population.[a]

Characteristic	Pre-eclampsia (n = 57)	Non pre-eclampsia (n = 63)	*P* value
Age, y	28.75 ± 6.15	28.13 ± 5.57	0.431
Length of pregnancy at admission, wk	33.32 ± 3.11	33.70 ± 3.14	0.693
Net urine protein excretion, mg			
4 h	73.56 ± 30.62	23.75 ± 9.49	0.001
8 h	143.25 ± 63.47	36.81 ± 12.5	0.001
12 h (day)	216.80 ± 92.57	60.55 ± 20.86	0.001
12 h (night)	204.32 ± 92.96	61.76 ± 17.87	0.001
24 h	421.12 ± 180.97	122.33 ± 35.9	0.001
Protein-to-creatinine ratio			
4 h	0.3210 ± 0.057	0.096 ± 0.055	0.001
8 h	0.3208 ± 0.058	0.101 ± 0.052	0.001
12 h (day)	0.3208 ± 0.058	0.098 ± 0.052	0.001
12 h (night)	0.3207 ± 0.057	0.094 ± 0.042	0.001
24 h	0.3208 ± 0.058	0.096 ± 0.046	0.001
Systolic blood pressure	152.04 ± 10.77	148.35 ± 6.82	0.001
Diastolic blood pressure	97.39 ± 8.07	95.33 ± 6.97	0.151
Parity			
Nulliparous	34 (60)	31 (49)	
Multiparous	23 (40)	32 (51)	

[a] Values are given as mean ± SD or number (percentage) unless stated otherwise.

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