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A Comparison of Urine Dipstick Test with Spot Urine Protein-Creatinine Ratio and 24 Hour Urine Protein Excretion in Women with Hypertensive Disorders of Pregnancy

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ABSTRACT

Background: Estimation of 24hour urine protein excretion and evaluation of spot protein- creatinine ratio in a random urine sample have been standard methods for determination of protein excretion. . The urine dipstick method, a semi-quantitative method of proteinuria estimation, has long been used as a screening tool for the same purpose. The objective of this study was to assess the efficacy of dipstick as a test for measurement of proteinuria in comparison with 24 hour urinary protein collection and spot urine protein/creatinine ratio as a screening test in pregnant patients with suspected hypertensive disorder of pregnancy attending an obstetric outpatient service.

Methods: 150 patients were recruited with suspected hypertensive disorders of pregnancy attending the obstetric outpatient service at our Department of Obstetrics and Gynecology and measured proteinuria in them by dipstick method, 24-hour urine protein collection and spot urine protein/creatinine ratio and calculated the degree of correlation between the first with the other two standard tests.

Results: The correlation of the urine dipstick test values with the 24-hour urine protein excretion was strong (r=0.757),but when compared to the spot urine protein-creatinine ratio, it was moderate (r=0.612). At 1+ grading of proteinuria, urine dipstick demonstrated greater sensitivity but at 2+ grading, dipstick was more specific in identification of significant proteinuria.

Conclusion: We conclude that dipstick as a test correlates better with 24 hour urine protein estimation than with the protein-creatinine ratio. Further, 1+ grading of urine dipstick could be a good screening tool for identifying proteinuria in patients attending the obstetrics outpatient service. However, the 2 + grading of the urine dipstick would be required to serve as an alternative to the 24-hour urine collection for detection of significant proteinuria or calculation of spot urine P/C ratio.

Key Words: *Preeclampsia, Proteinuria, 24 hour urine protein, spot urine protein-creatinine ratio, urine dipstick.*

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INTRODUCTION

Proteinuria occurs in preeclampsia as a consequence of reduction in the integrity of the glomerular barrier or reduced tubular reabsorption. It remains an important objective criterion for diagnosis of preeclampsia and has been used to classify the severity as well as to predict adverse fetomaternal outcome in preeclampsia[1]. It is a multisystem endothelial disease that leads to glomeruloendotheliosis and in severe cases, it may lead to renal impairment and failure. The presence of significant proteinuria predisposes a pregnant woman to coagulopathy, liver disease, and stroke. Serious perinatal morbidity occurs in the form of preterm delivery, often iatrogenic and fetal growth restriction[2]. Therefore, assessing the presence or absence of significant proteinuria (≥0.3 g/day) represents a key component in the evaluation of pregnant women with hypertension. Among the various methods available to quantify proteinuria, 24-hr urinary protein estimation remains the gold standard[3]. This test in itself is not without problems. The collection is cumbersome, time-consuming, inconvenient to patients as well as hospital staff, and subject to errors such as incomplete collection leading to inaccuracies. Alternative methods like a spot urine sample Protein- Creatinine (P/C) ratio avoid the influence of variations in urinary solute concentrations and can reduce the delay in diagnosis and management of preeclamptic patients. This approach is based on the fact that in presence of a stable glomerular filtration rate, urinary creatinine

excretion has been reported to be fairly constant in a given individual. However, routine examination of random spot urine samples is usually performed by semi-quantitative tests like urinary dipsticks. Though easy to perform, the urinary dipsticks indicate the approximate protein concentration at the time of sampling and fail to give an idea about the total daily excretion of protein. Thus, if the urine output in one day is much less or more than 1 litre, misinterpretation of result is likely to occur.

There are few studies which have examined urine samples from the outpatient department and evaluated the comparability of the P/C ratio and 24-h urine protein excretion with the dipstick method. One such study showed that the correlation between the protein/creatinine ratio and the corresponding dipstick value for albumin was statistically highly significant for all levels of proteinuria[4].

However, it must be remembered that a positive dipstick protein may be elevated due to other sources of protein, such as blood, semen or vaginal secretions in urine. Further, since it measures primarily albumin, the dipstick may occasionally be normal when significant quantities of other proteins are present in the urine. The aim of the present study was to compare the accuracy of dipstick test with spot urinary protein/creatinine ratio (P/C) and with the 24-hour urine protein excretion.

Methods

This study was carried out in pregnant women with hypertension attending the Department of Obstetrics and Gynecology, Jawaharlal Nehru Medical College, AMU, Aligarh. Eligible Patients were enrolled from November 2019 to October 2022. The study was approved by the Institutional Ethical committee.

- **Study design**
  Observational cross-sectional study
- **Sample size**
  One hundred and fifty eligible patients were recruited during the study.

Inclusion criteria

- Singleton pregnancy
- Age range between 20 and 40 years
- Gestational age > 20 weeks
- All patients with BP ≥ 140/90mmHg on at least two occasions taken 4hours apart.
- Proteinuria of ≥1+ as detected by dipstick test

Exclusion criteria

- History of chronic hypertension
- Development of proteinuria before conception
- Chronic renal disease
- Pathological vaginal discharge
- Bleeding per vaginum
- History of recurrent urinary tract infections
- Patients who require delivery before completion of collection of 24hr urine sample
- Multiple pregnancies

A thorough general and obstetric history were taken for every enrolled patient. Informed consent was obtained from all enrolled patients. Every patient was assessed with respect to general physical, systemic, and obstetric examination. All routine antenatal investigations (Blood group typing, hemoglobin estimation, Liver function test, Kidney Function Test, Urine routine examination, HIV testing, HBsAg testing, STS) were performed on admitted patients. Spot urinary protein-creatinine ratio was conducted in all patients. Additionally, 24-hour urine protein estimation was carried out in all patients as a gold standard test. Collection of 24-hour urine was begun in the morning after discarding the first voided urine of morning. Patients were directed to collect a second midstream urinary sample for evaluating spot urinary protein-creatinine ratio and qualitative urinary protein estimation was done by dipstick, graded as 1+ or 2+. The urine sample for spot PCR was collected in a clean bottle and patient was instructed to clean the perineal area with saline before sample collection.

The samples were analyzed in the Department of Medicine for the following:

- Measurement of 24hour urine protein was done by Esbach's method wherein an aliquot is taken from 24hour urinary sample and the reagent(10gm picric acid and 20gm citric acid to 1L distilled water)is added to it[5]. Compound is left standing for 24hours then. Precipitated protein is interpreted in gm/litre.
- Urine creatinine was detected by modified Jaffe's kinetic method.

- The urine protein and creatinine ratio was obtained by dividing the urine protein concentration (mg/dl) by the urine creatinine concentration (mg/dl). Reference ranges for protein/creatinine ratio was taken as <0.3 and ≥0.3. 24-hour urine protein excretion was graded into 3 groups: <300 mg, 300-1000 mg and >1000 mg. Dipstick was graded as 1 + and 2 +.

Statistical analysis

Collected data were entered into Microsoft excel and then into SPSS. Demographic data used descriptive statistics and was presented as mean,

±S.D., median and percentage, wherever appropriate. The relationship between the urine dipstick urinalysis with both spot protein creatinine ratio and 24 hour protein excretion respectively was estimated with Pearson's correlation test and the correlation coefficient was calculated which was expressed as "r". Inferential statistics were applied using chi-square test.

RESULTS

150 patients with hypertensive disorders of pregnancy who met the inclusion criteria were recruited for the study. The region and age wise distribution of patients are shown in (Table 1 and Table 2 respectively).

Table 1: Age distribution of studied patients

Age (years)	**1+ Dipstick**	**2+ Dipstick**	**Total**
≤ 20	2 (2%)	5 (10%)	7 (4.6%)
21-25	40 (40%)	15 (30%)	55 (36%)
26-30	50 (50%)	25 (50%)	75 (50%)
31-35	8 (8%)	3 (6%)	11 (7.3%)
>35	0	2 (4%)	2 (1.3%)
Total	100 (100%)	50 (100%)	150 (100%)

Table 2: Region wise distribution of studied patients

Address	1+ Dipstick	2+ Dipstick	Total
Rural	70(63%)	30(75%)	100(66%)
Urban	40(34%)	10(25%)	50(33%)
Total	110	40	150

Table 3 shows the distribution of patients with respect to period of gestation. 61.3% patients had urine dipstick analysis of 1+, 36.0% were in category 2+ while only 2.7% had significant proteinuria ranging between 300mg and 1000mg/day (urine dipstick 3+).

Table 3: distribution of patients with respect to periods of gestation

POG (weeks)	1+ Dipstick	2+ Dipstick	Total
28-32	10(9%)	10(25%)	20(13%)
33-36	55(50%)	25(62%)	80(53%)
37-40	45(41%)	5(12.5%)	50(33%)
Total	110	40	150

Table 4 shows association between 24hour urine protein and urine dipstick. Out of 92 patients with a urine dipstick value of 1+, 36 patients had 24hr urine protein ≤300, and 56 (60.9%) patients had 24hr urine protein between 301-2000. Out of 54 patients with urine dipstick of 2+, 53 patients had 24 hr urine protein between 301-2000 and similarly, 4 patients with dipstick value of 4+ had 3 patients with 24 hr urine protein >2000. This shows a significant association between urinary dipstick and 24hr urine protein ($p<0.001$). Similarly Table 5 shows association of spot PCR with urine dipstick. In a total of 150 patients, out of 92 patients with a dipstick value of 1+, 26 patients had UPCR of <0.3, and 66(71.7%) patients with UPCR >0.3. Similarly, out of 54 patients with urine dipstick 2+, 1 patient had UPCR <0.3 and 53(98.1) patients had UPCR >0.3. Likewise, all 4 patients with urine dipstick 3+ had UPCR >0.3. Thus, the association between urinary dipstick and spot urine protein-creatinine ratio is significant ($p<0.001$). A positive correlation was depicted by Pearson's correlation test between 24hour urine protein and dipstick test with $r=0.757$ and $p<0.01$ which was strongly significant (Table 6). However, correlation by Pearson's test between spot PCR and dipstick was moderate with $r=0.612$ with $p<0.01$ (Table 6).

Table 4: Association between urinary dipstick and 24-hour urine protein

DIPSTICK		24 HUP			Total	P-value
		≤300	301 – 2000	>2000		
1+	Number	36	56	0	92	<0.001
	%	39.1%	60.9%	0.0%	100.0%	
2+	Number	1	53	0	54	
	%	1.9%	98.1%	0.0%	100.0%	
3+	Number	0	1	3	4	
	%	0.0%	25.0%	75.0%	100.0%	
Total	Number	37	110	3	150	
	%	24.7%	73.3%	2.0%	100.0%	

Table 5: Association between urinary dipstick and spot PCR

			Spot PCR		Total	P-Value
			<0.3	≥0.3		
24 HUP	≤300	Number	23	14	37	<0.001
		%	62.2%	37.8%	100.0%	
	301 - 2000	Number	4	106	110	
		%	3.6%	96.4%	100.0%	
	>2000	Number	0	3	3	
		%	0.0%	100.0%	100.0%	
Total		Number	27	123	150	
		%	18.0%	82.0%	100.0%	

Table no 6: Correlation of Dipstick with 24 hrs. urinary protein and SPOT PCR

Correlations				
		DIPSTICK	24 HUP	SPOT PCR
DIPSTICK	Pearson Correlation (r)	1	.757**	.612**
	P value		.000	.000
	N	150	150	150
24 HUP	Pearson Correlation (r)	.757**	1	.734**
	P value	.000		.000
	N	150	150	150
SPOT PCR	Pearson Correlation (r)	.612**	.734**	1
	P value	.000	.000	
	N	150	150	150
**. Correlation is significant at the 0.01 level (2-tailed).				

		24 HUP
DIPSTICK	Pearson Correlation (r)	0.757**
	P-value	.000
	N	150

**. Correlation is significant at the 0.01 level (2-tailed).

		SPOT PCR
DIPSTICK	Pearson Correlation (r)	0.612**
	P-value	.000

	N	150

**. Correlation is significant at the 0.01 level (2-tailed).

DISCUSSION

The correlation of the dipstick method with standard urinary tests for women with hypertensive disorders of pregnancy such as the spot urine P/C ratio and the 24-h urine protein excretion showed that the dipstick method correlated more strongly (r = 0.757) with the 24-h urine protein excretion method as compared to a moderate correlation (r = 0.612) with the urine P/C ratio. Because of its high sensitivity, the 1 + urine dipstick level seems to be useful as a screening test for spot urine samples for the presence of protein if the patient is having suspected hypertensive disorder of pregnancy. Urine dipstick appears to be more specific for estimation of proteinuria at the 2+ dipstick level, but could grossly underperform if this level were to be used as a screening test. Further, our study was conducted in patients without any pre-existing renal disorder, and in patients who have such disorders a quantitative test would definitely be required.

Our results depict that the convenience of using only qualitative tests for urinary protein estimation such as dipsticks may sacrifice the accuracy of diagnosis of proteinuria and potentially compromise the safety of the patient and her pregnancy. While these tests may be used in the routine screening of normal pregnant women, but quantitative tests may be better options in subjects in whom early and definitive diagnosis of proteinuria is important, e.g. in suspected cases of hypertensive pregnancies, preeclampsia, and HELLP (Hemolysis, Elevated Liver enzymes, and Low Platelet count) syndrome.

Significant proteinuria is defined by the International Society for the Study of Hypertension in Pregnancy as excretion of ≥300 mg of protein in a 24-h urine specimen. Thus, the gold standard for diagnosis of significant proteinuria is based on a 24-h urine collection. This test in itself is not without problems. The collection is cumbersome, time-consuming, inconvenient to patients as well as hospital staff, and subject to errors such as incomplete collection leading to inaccuracies. Hence a spot urine examination would be more acceptable and less time consuming. The usefulness of spot urine sampling using the protein/creatinine ratio and dipstick test was thus tested against the commonly used 24-hour urine protein excretion.

The P/C ratio takes into account the fact that creatinine excretion remains fairly constant in the presence of a stable GFR. The protein excretion would also likewise be fairly stable. Hence the ratio of the two in a single voided sample would reflect the cumulative protein excretion over the day, as the two stable rates would cancel out the time factor.

In a study on 26 children below 12 years of age, having nephrotic syndrome, the correlation between the P/C ratio and the corresponding dipstick value for albumin was statistically highly significant (P ≤0.001) for all levels of proteinuria. In this study, the urine sample soon after the first voided urine in morning was taken for calculating spot PCR and dipstick similar to our present study. Further sample collection for the 24-h urine started from the second urine sample till the first urine sample the next day morning.

The spot UPCR is a method of rapid quantitative assessment of proteinuria. All patients had normal creatinine clearance as estimated by serum creatinine and height index. However the random dipstick test was reliable only when significant proteinuria was present. It did not correlate well when the proteinuria was in the lower range. Correlation with creatinine clearance was not looked at. In the presence of stable renal function a P/C ratio of less than 0.3 can be taken to be within normal limits. Reports from previous studies on dipstick test have suggested that, neither the presence nor severity of proteinuria can be confidently predicted by such method alone.

In our study, where dipstick readings were of the order of 1 +, there was a high incidence of false positives when compared to both 24-h urine protein and the spot urinary P/C ratio, though it should be emphasized that dipstick readings of 2 + correctly predicted the presence of significant proteinuria in most cases. The urine dipstick test currently used is semi- quantitative. Also as stated above, compared with the quantitative methods there is sensitivity limitations with dipstick tests. **Waugh et al**[6] reported 51% and 78% as the respective sensitivity and specificity of urine dipstick. The other reported sensitivity for visual urine dipstick widely varies from 51% to 85%. If one uses automated analyzer higher accuracy may be obtained. The urinary protein results can also be affected by variations in sample concentrations. The grading of urinary dipstick can vary depending upon maternal hydration status. Thus, physicians cannot distinguish between pathological proteinuria and false positives caused by concentrated samples when the urinary protein report shows less than 1 + or "trace". The spot urine P/C ratio can act as an indicator to detect over-diluted samples which have less than 10 mg/dL of urinary creatinine. When negative protein results are found in over-diluted samples, the samples should be re-collected and re- examined to ensure accurate results. It indicates that without the spot urine P/C ratio, the diagnosis of proteinuria will be underestimated because of false negative results. Since conventional dipsticks have sensitivity and specificity limitations, the urinary protein results could be false positive or false negative. If the false results are not detected, the consequences can be serious due to delays in diagnosis and treatment. However, it is costly to retest false negative data. Our data seems to suggest that urinalysis with the dipstick test is reasonably specific at the 2 + level, but at its most sensitive diagnostic level (1+) it will over-diagnose hypertensive disorders of preeclampsia.

On the basis of results interpreted from our study, we recommend that in patients with suspected preeclampsia, an initial screening with dipstick urinalysis should be performed. If the urinalysis shows 2 + protein or greater, the patient most likely has significant proteinuria but if the urinalysis is negative for protein or is 1 +, spot urine P/C ratio should be ordered to further define the risk. If the urine P/C ratio is ≥0.3, the patient most likely has significant proteinuria. If the urine protein–creatinine ratio is <0.3, further evaluation with a 24-h urine collection may be required.

This systematic approach would be better at providing more accurate, earlier as well as cost-effective diagnostic information than the traditional dipstick urinalysis alone. With the traditional urinalysis by dipstick, using ≥1 + as a cutoff, the presence of significant proteinuria may be over-diagnosed. Owing to the greater numbers of false positives with 1+ proteinuria, compared to both 24-h urine protein excretion and the spot urine P/C ratio, dipstick test may not be effective in deciding definitely, which patients need to be managed as preeclamptics. Using the dipstick test combined with the urine P/C ratio and the 24-h urine protein excretion in a strategy as mentioned above, absence or presence of significant proteinuria may be more timely and cost-effectively determined. In many cases, precise assessment of the degree of proteinuria is not required. Rather, the clinician is more keen in classifying patients into broad categories by the degree of proteinuria, in order to decide which patient requires further investigation. In this study we found that the correlation between the dipstick test with the 24-h urinary protein excretion was stronger than with the spot urinary P/C ratio. However to be of practical value, the 1 + level of dipstick may require further investigation with quantitative testing, whereas at the 2 + level on the dipstick, most patients would be having significant proteinuria which may or may not require further investigations at the discretion of the clinician. A wider application of this techniques seems useful in view of its advantages in terms of time, increased patient convenience, and reduced costs.

CONCLUSION

Based on the findings of the present study, we may conclude that a urine dipstick test correlates strongly with 24-hour urine protein excretion and moderately with the urine P/C ratio. This test at the 2 + level, may therefore be an alternative to the 24-hour urine collection for detection of significant proteinuria or calculation of spot urine P/C ratio for screening pregnant women with suspected hypertensive disorders of pregnancy, attending the obstetric outpatient department. However, patients with 1+ proteinuria, need to undergo further quantitative testing for reliably stratifying their degree of proteinuria.

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