# Protein/Creatinine Ratio In Random Urine Specimens For Quantitation Of Proteinuria In Pre-Eclampsia

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**Citation**

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**Abstract**

Objective: The purpose of this study is to determine if a patient's protein values using the protein /creatinine ratio correlates with the 24- hour value to confirm the diagnosis of preeclampsia.

Study Design: The study population included 86 patients with hypertensive disorders of pregnancy. Patients' urine was collected over 24 hours. The urine volume, and total protein in the 24-hour samples was evaluated. Urine distick test and the Protein /creatinine ratio in a spot urine sample were compared to the 24-hour results. The test of validity and reliability was done using the sensitivity, specificity, false positive and the false negative rate. Also assessed were the positive and negative predictive value and the accuracy.

Results: Eighty-six pregnant patients completed the study. There was a strong correlation between the random urinary protein-to-creatinine ratio and the quantitation of 24-hour proteinuria.

Conclusion: The presented data support a strong correlation between random urinary protein-to-creatinine ratio and quantitation of 24-hour proteinuria in hospitalized pregnant patients with preeclampsia.

## INTRODUCTION

Hypertensive disease complicates 7% of pregnancies and is classified according to preexisting chronic hypertension or pregnancy-induced hypertension with or without

proteinuria. The diagnosis of preeclampsia is determined by the presence of hypertension accompanied by proteinuria, evident after 20 weeks' gestation[1, 2]

Pre-eclampsia/ Eclampsia is an important cause of maternal morbidity and mortality[3,4,5] as well as a significant contributor to increased perinatal morbidity and mortality rates in Nigeria[6,7]. Twelve percent of all maternal deaths worldwide are due to hypertensive disorders of pregnancy, [5] and it has been shown that patients with significant proteinuria have a significant reduction in the mean birth weight for gestational age compared to patients with hypertension alone due to intrauterine growth restriction. In contrast, in women with hypertension alone, the mean birth weight for gestational age is the same as that in normotensive women[8]. Early detection and prompt management of patients with proteinuria is therefore beneficial to the patient and the fetus[9, 10, 11, 12].

The gold standard for measuring proteinuria is a 24-hour urine sample for total protein; patients with hypertension have only <300 mg, those with mild preeclampsia have 300 mg to 5000 mg, and those with severe preeclampsia have >5000 mg of protein[13] . The 24-hour period required for collection of the urine may result in a delay in diagnosis and treatment or possibly a prolonged hospital stay. Shortening the period for the diagnosis of preeclampsia would be valuable for management purposes, as well as for decreasing hospital cost and patient inconvenience. Again in most clinical situations, a 24hour delay before definitive decisions on appropriate management may increase maternal and perinatal morbidity and mortality. Besides, the collection is cumbersome often incomplete and is difficult to administer on out patients. Unfortunately, the most widely used screening test for proteinuria, the dipstick test, has been found to be fraught with error and correlates poorly with 24 hour urinary protein excretion[13, 14, 15, 16]. Nevertheless, in the

absence of a convenient, easy to administer but more accurate test for proteinuria, dipstick tests remain the mainstay of screening for proteinuria worldwide. Several investigators have previously reported other rapid methods of identifying proteinuria such as measurements of urine protein from 8- and 12-hour samples.4-6. These methods have not been shown to correlate with disease severity as determined by the results of 24-hour collection.

There remains therefore the need for a reliable quantitative measurement of urinary protein excretion that will be quick, easy to administer and correlate well with 24hour urinary protein excretion. The use of the urinary protein /creatinine ratio has been extensively demonstrated to posses the potential to fill this vacuum in non-pregnant patients[17, 18, 19, 20] with proteinuria. A few studies have also shown its usefulness among Caucasian hypertensive pregnant women[16, 21]. Studies in this environment have been fewer still. This study aims to evaluate the diagnostic value of Protein/creatinine ratio in single voided urine samples for quantitation of proteinuria compared to those of a 24-hour sample in patients with preeclampsia

## MATERIAL AND METHODS

All pregnant patients who were >20 weeks' gestation who had provided a 24-hour urine sample for protein/ creatinine clearance as ordered by their physicians to rule out preeclampsia were included in the study. Participants in the study were inpatients Eighty-Six consecutive cases were recruited into the study. The patients were on modified bed rest in the hospital. The hospital ethical committee determined that consent was not required for patient participation

Exclusion criteria included all cases of chronic hypertension, chronic renal disease, pathological vaginal discharge, urinary tract infection, and patients that had vulva or vaginal cleansing with antiseptics or skin cleansers like chlorhexidine. Patient who required delivery before completion of collection of the 24 hour urine sample were also excluded.

Diagnosis of hypertension was based on two consecutive measurements of diastolic blood pressure of 90mmHg 4 hours or more apart, one measurement of diastolic pressure of 110mmHg or more or a rise of 30mmHg or 15mmHg above normal pre-pregnancy systolic and diastolic blood pressures respectively[13, 22],, after 20th week of pregnancy taken in the sitting position, using an appropriate sized cuff and korotkoff phase V (disappearance of sound) as the diastolic blood pressure[23, 24, 25, 26].

Total urine collection time was 24 hours. Inpatients had the assistance of the nursing staff for collection. Each container was marked with the patient's name, number of the container, and collection time. A protein /creatinine ratio and a urine dipstick test for protein was done on a random urine sample within the 24-hour period.

Urine dipstick test: The dipstick tests were done using the multistix 10SG urinalysis strip. Significant proteinuria is defined as two random clean catch or catheter urine specimens with 2+ (1g albumin/L) or more on a reagent strip or 1+ (0.3g Albumin/L) if the specific gravity is less than 1030 and pH less than 8[23].

24 hour urine Protein. The urine was stirred to ensure homogeneity and a 6-mL aliquot sample was obtained. Analysis for protein was performed by using a modified Fujita method (Sigma Diagnostics Microprotein-PR, procedure No. 611).[27] This assay measures the shift in the absorption that occurs when the pyrogallol red-molybdate complex in the reagent binds basic amino acid groups of protein molecules. The total urinary protein (mg/day) was determined by multiplying the total urine volume (dL) by the concentration of protein in the test sample (mg/dL). Each sample was run in duplicate and the mean value was used in the calculations. Samples were run with low and high controls. Comparison of this assay with other similar commercially available reagents shows a correlation coefficient of 0.997 for samples containing 1 mg/dL to 128 mg/dL. For those samples with significant proteinuria that exceed this value, the urine was diluted 1:10 with deionized water to maintain the sensitivity of the assay. Significant proteinuria was defined by one 24 hour urine collection with total protein excretion of 300mg and more.

Creatinine. The urinary creatinine was done using the modified Jaffe Method as outlined by the manufacturers of the Kit, Quimica Clinical Applicada S.A. Spain 2000. The test was based on the principle that at alkaline pH values, creatinine reacts with Picric acid to produce a coloured compound, creatine alkaline picrate, which can be photometrically measured[28].The serum creatinine was determined by using the same assay with 300 µL of serum. Estimation of The creatinine clearance was calculated by using the following formula:

Creatinine clearance = Urine creatinine (mg/dL) x Volume (mL)/Serum creatinine (mg/dL) x Time (min)

The tests were performed by a biochemist working in the laboratory of the hospital who was co-opted into the study. For each patient, information on the age, parity and gestational age were obtained. Based on the results, the sensitivity, specificity, the false positive and false negative rates, positive predictive value, negative predictive value and accuracy were determined when the dipstick protein estimation and the spot protein/creatinine ratio estimation were compared with the 24 hour protein estimation.

All data were entered into the computer and analysed using the EPI Info Software.

## RESULTS

There were a total of inpatients 86 with 86 urine samples. Collection of urine started at 9 am. Table I shows demographic data for the patients. Of the 86 subjects recruited for the study, the age group 20-29 contributed the highest percentage (75.6%), followed by age group 30-39 (18.6%). Majority of the subjects were nulliparas (54.7%), followed by primiparas (15.1%). Most of the fetuses were at term (74.4%).

The sensitivity of the various tests showed that the protein/creatinine ratio was the highest with sensitivity of 92%, while the sensitivity of urine dipstick was 81%. The false negative rate was also highest with the dipstick test (19%), while the protein/creatinine ratio was 8%. The specificity for the protein/creatinine ratio was 86%, while that for the urine dipstick test was 47%. The false positive rate was highest with the dipstick test (53%), that for the protein/creatinine ratio 14%.

The positive predictive value for the protein/creatinine ratio was 83% and low with the dipstick test (59%). The positive predictive value of the two tests in combination was 90%. The Negative predictive value for protein/creatinine ratio was 93%, while that for the urinary dipstick test (71%). The accuracy of the protein/creatinine ratio was 88% and the least accurate was dipstick test (63%).

In terms of cost, the cheapest test is the dipstick test ($ 1) which is also the quickest to carry out (immediately). The protein/creatinine ratio was more expensive ($ 5) which took about 30minutes to carry out. The 24hr protein estimation cost $3 and result is available about 25 hours

**Figure 1**

Table 1: Age, Parity And Gestational Age Of Patients

| AGE(YEARS) | YEARS | NUMBER | PERCENTAGE |
|---|---|---|---|
| | <20 | 5 | 5.8 |
| | 20-29 | 65 | 75.6 |
| | 30-39 | 16 | 18.6 |
| | >39 | 0 | 0 |
| PARITY | 0 | 47 | 54.7 |
| | 1 | 13 | 15.1 |
| | 2 | 10 | 11.6 |
| | 3 | 5 | 5.8 |
| | 4 | 5 | 5.8 |
| | >4 | 6 | 6.9 |
| GESTATIONAL AGE(WEEKS) | <34 | 6 | 6.9 |
| | 34-<37 | 16 | 18.6 |
| | 37-<42 | 64 | 74.4 |
| | >42 | 0 | 0 |

**Figure 2**

Table 2: Comparison of urinary dipstick with 24hour protein estimation.

| | 24 HOUR PROTEIN | | | | |
|---|---|---|---|---|---|
| DIPSTICK | Positive (>300mg) | | Negative(<300mg) | | Total |
| Positive (3+) | TP | 17 | FP | 6 | TP + FP 23 |
| Negative (1+) | FN | 6 | TN | 15 | FN + TN 21 |
| Total | TP + FN | 23 | FP + TN | 21 | |

**Figure 3**

Table 3: Comparison of protein/creatinine ratio with 24-hr protein estimations.

| | 24 HOUR PROTEIN | | | | |
|---|---|---|---|---|---|
| P/C ratio | Positive (>300mg) | | Negative(<300mg) | | Total |
| Positive P/C (>30) | (TP) | 33 | (FP) | 7 | TP + FP 40 |
| NegativeP/C (<30) | (FN) | 3 | (TN) | 43 | FN + TN 46 |
| Total | TP + FN | 36 | FP+TN | 50 | |

**Figure 4**

Table 4: Measure of Reliability and Validity of the two tests

| Test of Validity | Dipstick | P/C Ratio |
|---|---|---|
| Sensitivity | 81% | 92% |
| Specificity | 47% | 86% |
| Positive Predictive Value | 59% | 83% |
| NegativePredictive Value | 71% | 93% |
| False Positive Rate | 53% | 14% |
| False NegativeRate | 19% | 8% |
| Accuracy | 63% | 88% |

## DISCUSSION

The socio-demographic variables shows that the peak age range was 20-29 years (75.6%), primigravidae contributed the commonest parity (54.7%) and the peak gestational age was at term (74.4%). Primigravidae have been demonstrated by numerous workers to be at high risk of developing pre-eclampsia[29, 30]. The peak age of 20-29 years may be reflective of the fact that most first deliveries in this environment occur at that age and not necessarily of any special contribution of this age bracket to the aetiology of the disease. Majority of the deliveries occur at term hence the 74.4% that had their deliveries at term is not surprising.

The quantitation of proteinuria in preeclampsia is necessary for diagnosing preeclampsia and for classifying mild versus severe disease. It is postulated that protein excretion varies throughout the day, which is thought to be secondary to vasoconstriction and vascular spasm producing a fluctuation in protein from moment to moment. Protein excretion tends to increase with ambulation and upright body position, which produces renal vasoconstriction and altered permeability of the glomerular barrier[31]. These physiologic factors are thought to produce a diurnal variation in protein excretion. It is known that albumin excretion has a circadian rhythm that makes a 24- hour collection necessary[32]. The proteins excreted in urine of preeclamptic women are, however, heterogeneous and variable and in some cases do not even include albumin[33]. Currently the 24-hour urine is the gold standard for the evaluation of proteinuria. A shorter period to diagnosis would have clinical benefits such as shortened time to delivery and earlier use of antenatal glucocorticoids. A more expedient intervention could decrease perinatal morbidity. Certainly, those women without preeclampsia would be discharged to home earlier if a more rapid (and accurate) determination of proteinuria was available, thus resulting in lower health care costs. Patient compliance with testing may also improve if the test for proteinuria can be simplified or shortened.

Several investigators have explored other means of quantifying proteinuria in a shorter period. In this study a comparison of the Protein/Creatinine ratio, and the urinary dipstick test with the standard 24hour protein estimation using the various indices of validity was quite revealing. Sensitivity, Specificity, Positive and Negative predictive Values, and False Positive and Negative rates were the indices used.

Sensitivity sometimes termed the detection rate is the ability of a test to find those with the disease or the proportion of true positive correctly identified. The sensitivity of a diagnostic test is the probability that patients with significant proteinuria (as assessed by 24 hour urine protein estimation) will have a positive test result,. In this study, the protein/creatinine ratio with a sensitivity of 92% allows the clinician to correctly identify greater than 9 out of 10 cases of significant proteinuria.

This implies early diagnosis of preeclampsia in that proportion of patients. The sensitivity of urine dipstick was much lower at 81%. The sensitivity is a measure of the False Negative Rate, which is a measure the probability that patients with significant proteinuria will have a negative test result. It is a measure of the proportion of times the test will test negative for protein when the converse is the case. This is expectedly lower for the protein/ creatinine ratio at 8%. Missed diagnosis of preeclampsia is higher with the urine dipstick test emphasising the drawback of relying on it in a clinical setting. Reason for the low sensitivity is because of this: The detecting chromophore is tetrabromophenol blue, which, changes from yellow-green (-) to blue-green (+++) when viewed against a while background in natural light. However, dipstix testing has been demonstrated to be highly observer dependent and in studies have been found to have a high false positive rate and false negative rate despite the use of experienced observers This means with the urine dipstick test up to one quarter of patients in whom protein is not detected by dipstick have significant proteinuria. Thus many patients that may need urgent intervention will be undetected. And the disease which is a multi-systemic one may worsen and patients present later with marked materno-fetal complications. The false negative rate of 19% for dipstick test found in this study is similar to a rate of 18% reported in a Caucasian population.

Specificity of a diagnostic test is the probability that patient

without significant proteinuria will have a negative test result. The urine dipstick had the lowest specificity of 47%. The protein/ creatinine ratio has a specificity of 86% a false positive rate of 14%. Dipstick tests had a false positive rate of 53% which is over three times that of the spot urinary protein/creatinine ratio (14%). This implies that greater than 50% of patients without proteinuria are incorrectly identified in a clinical setting if urine dipstick test is relied upon. This is in agreement with numerous studies that have demonstrated that false positive reactions may occur with concentrated urine, highly alkaline urine (pH>8), contamination of urine with vaginal discharge and antiseptics like chlorhexidine.

The result clearly demonstrates that a positive result on dipstick is unreliable for clinical decision making. While the false positive rate for the urinary protein/creatinine ratio of 14% still leaves room for errors in diagnosis and premature intervention; a positive test is more reliable than that of a dipstick reaction. The use of dipstick test will be associated with an over diagnosis of proteinuria, which is misleading and in a significant number of cases causes unnecessary interventions with increased risk of interventional morbidity and mortality from the complications of induction of labour like hyperstimulation, fetal distress, ruptured uteri and prematurity with all its adverse perinatal outcome. The surgical and anaesthetic complications of emergency caesarean section are well recognised and these are most regrettable if they occur due to interventions that were not really necessary due to false positive results. The high specificity shown by the protein/creatinine ratio, will accurately diagnose pre-eclampsia and thus prevent unnecessary interventions.

It has been suggested that sensitivity and specificity are not as useful to the clinician as the positive and negative predictive value of the tests. This is because while sensitivity and specificity (population measures) look backward at results gathered overtime, clinicians have to interpret individual test results to those tested. Thus, what clinicians need to know are the predictive values of the tests.

The clinician and the patient need to know what the probability is that a positive result is genuinely positive (positive predictive value) and what the probability is that a negative result is genuinely negative. This determines the confidence the clinician has in a positive or negative result and his willingness to base clinical judgements on the results. The positive predictive values for urinary protein/creatinine ratio (83%), is higher than that for the dipstick test (48%). The positive predictive value is even higher when these indices are combined together. Hence the probability that a positive result with dipstick is false is higher than the probability that it is genuinely positive. This clearly shows the risk associated with making decisions based on a positive dipstick reaction. The positive predictive value demonstrates the unreliability of the dipstick test. This demonstrates that the possibility of mismanagement of patients based on decision made using a positive urinary protein/creatinine ratio is low.

The negative predictive value of dipstick is higher than its positive predictive value (71% versus 59%). This has significant implications for clinical practice. Hence the probability that a negative dipstick reaction is genuinely negative is much higher than the probability that a positive result is positive-a negative result is more reliable than a positive one. However, the negative predictive value of dipstick test was found to be lower (71%) than for the protein/creatinine ratio (93%), hence, a negative result with these rapid diagnostic tests has a higher probability of being genuinely negative. In terms of accuracy which is the measure of a test to accurately detect or rule out the disease, this was expectedly higher for the protein/ creatinine ratio (88%) compared to the urine dipstick test(63%).

While effectiveness or validity of a test is very important, it is also crucial that it be affordable by those that need it as well as being easy to administer and the results been available early enough to aid clinical decision making. A cost and time analysis of the methods of quantifying proteinuria was done . It shows that dipstick tests are relatively cheaper, easier to administer and results are available immediately. This is responsible for its current widespread use as the commonest means of quantifying proteinuria; the protein/creatinine ratio is almost 5 times the cost of urinary dipstick. The result of the urinary dipstick result is gotten immediately, while the protein/creatinine ratio result is obtained in 30 minutes. When compared with the 24hr protein estimation whose result takes about 25 hours to get, the above methods are faster and are within safe limits to aid accurate diagnosis and treatment. The time required before a 24 hour urine protein is available as well as the difficulties in ensuring complete collection make it unfit for routine use in clinical practice.

The urine dipstick test is very unreliable lacking in accuracy reliability and validity. The advantage of the dipstick test is that it can be done anywhere by any trained paramedical or medical personnel while the urinary protein/creatinine ratio,

require laboratories and trained laboratory personnel. The protein/creatinine ratio of a single urine sample from pregnant women has been shown to correlate significantly with a 24-hour collection for patients with proteinuria.

The result of this study demonstrate that in hospital with appropriate laboratory personnel and where patients can afford it, routine use of either the protein/creatinine ratio for quantitation of proteinuria in patients with pre-eclampsia could be adopted. The continued use of the dipstick for the screening and diagnosis of preeclampsia cannot be justified. Continued dependence on it especially in clinical setting is fraught with hazards. There is an urgent need for its replacement with test such as the protein/creatinine ratio which has better correlation with the 24 hour urine protein. The protein/creatinine ratio especially is reliable, relatively faster and accurate for proteinuria correlating well with 24hour urinary protein excretion; they also show that it is much more reliable than the dipstick test on every test of effectiveness measured, and therefore should substitute the urine dipstick test for protein estimation in clinical practice.

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