ACCURACY OF THE SPOT URINARY MICROALBUMINURIA: CREATININE RATIO COMPARED TO 24 - HOUR URINE PROTEIN IN DETECTING PROTEINURIA IN PRE-ECLAMPSIA

A DISSERTATION SUBMITTED TO THE NATIONAL POST GRADUATE MEDICAL COLLEGE OF NIGERIA FOR THE PART TWO FELLOWSHIP EXAMINATION OF THE FACULTY OF OBSTETRICS AND GYNAECOLOGY

BY

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DECLARATION

I hereby declare that this work is original unless otherwise acknowledged. It has neither been presented to any College, Faculty or School for the award of a degree or diploma or fellowship nor has it been submitted elsewhere for publication.

Ekwedigwe, Kenneth Chinedu

Signature and Date

________________________________________
CERTIFICATION

We hereby certify that this work was carried out by Dr Ekwedigwe Kenneth Chinedu of the Department of Obstetrics and Gynaecology, Irrua Specialist Teaching Hospital, Irrua under our supervision.

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DEDICATION

I wish to dedicate this project firstly to God almighty who has granted me wisdom and grace thus far, and to my mother, brothers, sisters and my beloved wife and children. Moreso, to my late father – Chief Ekwedigwe Thaddeus who did so much for me to achieve my dreams in life.
ACKNOWLEDGEMENT

I wish to specially appreciate and thank Dr J. O. Eigbefoh and Dr. R. Eifediyi for making this project possible. I thank them for their supervision and motivation.

I also want to acknowledge all the Consultants and residents in the department. Most especially Drs G. Okome, S.A. Okogbenin and F. Omorogbe for their constructive criticisms and suggestions during the writing of this proposal. I also thank Mr Eboh Joseph and Mr Uyi of the Chemical Pathology Department for their cooperation in assisting with the tests. My special thanks also go to Dr Eliboh M. Osazebemide and Miss Ike Linda. May God bless you all.
### LIST OF ABBREVIATION

<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ISTH</td>
<td>Irrua Specialist Teaching Hospital</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<td>%</td>
<td>Per cent</td>
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<tr>
<td>BP</td>
<td>Blood Pressure</td>
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<td>SBP</td>
<td>Systolic Blood Pressure</td>
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<td>DPB</td>
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<td>MAP</td>
<td>Mean Arterial Pressure</td>
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<td>LMP</td>
<td>Last Menstrual Period</td>
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<td>GA</td>
<td>Gestational Age</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>PIH</td>
<td>Pregnancy Induced Hypertension</td>
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<td>PE</td>
<td>Pre-Eclampsia</td>
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<tr>
<td>mmHg</td>
<td>Millimeters of mercury</td>
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<td>mmol/L</td>
<td>Millimole per Litre</td>
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<td>mg/mmol</td>
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<td>µg/min</td>
<td>Microgramme per minute</td>
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<td>g/24 hours</td>
<td>Gramme per 24 hours</td>
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<td>mg/24hours</td>
<td>Milligramme per 24 hours</td>
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<tr>
<td>mg/g creatinine</td>
<td>Milligramme per grammecreatinine</td>
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<td>ml/min</td>
<td>Millilitre per minute</td>
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<td>mg/L</td>
<td>Milligramme per Litre</td>
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**NORMAL LABORATORY VALUES AT ISTH IRRUA**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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<tr>
<td>Urinary Creatinine</td>
<td>1.5 - 2.5 g/24 hours</td>
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<tr>
<td>Serum Creatinine</td>
<td>0.7-1.4 mg/dl</td>
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<td>Creatinine Clearance</td>
<td>100 -140 ml/min</td>
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<td>Microalbumin</td>
<td>&lt; 20 mg/L</td>
</tr>
<tr>
<td>Microalbumin/Creatinine Ratio</td>
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<tr>
<td>24 Hour Urinary Protein</td>
<td>&lt; 0.3g/24 hours</td>
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ETHICAL COMMITTEE’S APPROVAL

IRRUA SPECIALIST TEACHING HOSPITAL
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Research and Ethics Committee,

Irrua Specialist Teaching Hospital,

Irrua.

February 20, 2011.

Dr. Ekweigwe Kenneth Chinedu,
Department of Obstetrics and Gynaecology,
I.S.T.H,
Irrua.

Notification of Ethical Approval

On behalf of the Research and Ethics Committee, I wish to convey favourable ethical approval for the conduct of the research titled: “Accuracy of spot urinary microalbumin: creatinine ratio compared to visual dipsticks and 24 hour urine protein in detecting proteinuria in pre-eclampsia” at Irrua Specialist Teaching Hospital (ISTH).

Best wishes.

Dr. P.O Okohere
Chairman, Research and Ethics Committee.
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SUMMARY

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

Study Design: The study population included 80 patients with hypertensive disorders of pregnancy. Patients' urine were collected over 24 hours. The urine volume, and total protein in the 24-hour samples were evaluated. Urine dipstick test and the microalbuminuria/creatinine ratio in a spot urine sample were compared to the 24-hour results. The test of validity and reliability were 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 pregnant patients completed the study. The visual dipstick has a sensitivity of 72.1%, specificity of 68.4%, positive predictive value (PPV) of 88%, negative predictive value (NPV) of 43.3%, false positive rate (FPR) of 31.6%, false negative rate (FNR) of 27.9%, and accuracy of 71.3%. The urinary microalbumin dipsticks had sensitivity of 98.4%, specificity of 36.4%, PPV of 83.3%, NPV of 87.5%, FPR of 63.2%, FNR of 1.6%, and accuracy of 83.8%. The urinary microalbumin:creatinine ratio has sensitivity of 95.1%, specificity of 89.5%, PPV of 96.7%, NPV of 85%, FPR of 10.5%, FNR of 4.9%, and accuracy of 93.8%. The result showed a strong correlation between the random urinary microalbumin-to-creatinine ratio and the quantitation of 24-hour proteinuria.

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

Introduction

Hypertensive in pregnancy is a significant management problem for every obstetrician. It complicates 5-10% of pregnancies. In a minority of cases it is associated with proteinuria, and this usually indicates a multisystem disease, also known as pre-eclampsia.\textsuperscript{1,2} The diagnosis of pre-eclampsia is determined by the presence of hypertension accompanied by proteinuria, evident after 20 weeks gestation.\textsuperscript{1,2}

Pre-eclampsia/eclampsia is an important cause of maternal morbidity and mortality\textsuperscript{3,4,5} as well as a significant contributor to increased perinatal morbidity and mortality rate in Nigeria.\textsuperscript{6,7} Twelve percent of all maternal deaths worldwide are due to hypertensive disorders of pregnancy,\textsuperscript{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 intra-uterine growth restriction. In contrast, in women with hypertension alone, the mean birth weight for gestational age is the same as that in normotensive women.\textsuperscript{8}

Early detection and prompt management of patients with proteinuria is therefore beneficial to the patients and the fetus.\textsuperscript{9-12}
The gold standard for measuring proteinuria is 24-hour urinary protein, this is because of variation in protein excretion during the day, which is affected by factors such as water intake and excretion, rate of diuresis, exercise, recumbency and diet.\textsuperscript{13} However the major problem with 24 hour urine collection is that it is often impractical in the outpatient setting with problems of incomplete collection, delay in diagnosis and treatment and prolonged hospital stay.\textsuperscript{13} Shortening the period for the diagnosis of pre-eclampsia would be valuable for management purposes, as well as for decreasing cost and patient inconvenience. 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.\textsuperscript{13-16}

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 2hour, 8hour and 12hour samples and even protein:creatinine ratio in single voided urine samples. These methods have not been shown to correlate with disease severity as determined by the results of 24-hour urine collection. However, studies carried out by Eigbefoh et al showed some degree of correlation between protein-creatinine ratio and 24-hour urine collection, though, it was
expensive when compared with urine dipstick and require appropriate laboratory personnel.\textsuperscript{22}

Consequently, there is need for a reliable quantitative measurement of urinary protein excretion that will be quick, easy to administer and correlates well with 24-hour urinary protein excretion. The use of urine microalbumin and microalbumin/creatinine ratio posses the potential to fill this vacuum. It has been demonstrated that albuminuria in excess of 15mg/100mls or 300mg/day are usually associated with either pre-eclampsia or underlying renal disease.\textsuperscript{35} Also the urinary albumin excretion can be 10-20 times higher than normal, without being detected by conventional dipstick or laboratory test.\textsuperscript{38} A few studies have also shown its usefulness among Caucasian hypertensive pregnant women.\textsuperscript{36,37} Studies in this environment have been very few if any. This study aimed to evaluate the accuracy of using urinary microalbumin/creatinine ratio in single voided urine samples compare to 24-hour urine sample in detecting proteinuria in pre-eclampsia.
LITERATURE REVIEW
DEFINITIONS AND INCIDENCE

Pre-eclampsia is a hypertensive disorder unique to pregnancy, it is
the occurrence of hypertension and proteinuria developing usually after
20 weeks of pregnancy, during labour and the puerperium in a previously
normotensive, non-proteinuric woman.\(^1\)

Eclampsia is defined as the occurrence of generalized tonic-clonic
convulsion usually after the 20\(^{th}\) week of pregnancy, during labour and
the first 14 days of the puerperium, in absence of epilepsy and other
cerebral causes of convulsions.\(^53\)

Pre-eclampsia and eclampsia are major causes of maternal and
perinatal morbidity and mortality. It accounts for near 100,000 of the
over half a million annual maternal deaths worldwide.\(^83\) It is now the
leading cause of maternal mortality in Nigeria.\(^64\) In Irrua Specialist
Teaching Hospital, it accounts for 20\% of maternal mortality.\(^23\)

Risk Factors

Various risk factors have been identified in women with pre-
eclampsia. These include genetic, obstetrics and medical factors. Women
whose mothers and sisters had pre-eclampsia, have increased risk of
developing pre-eclampsia compared to the general population.\(^85\) Also,
African-Americans (negroids), have an increased risk compared to their
Caucasian counterparts.\(^85\)
The obstetric risk factors include primigravidity, multiple gestation, previous pre-eclampsia, hydrops fetalis with a large placenta and hydatidiform mole. The medical risk factors are chronic hypertension, chronic renal disease, diabetes mellitus, anti-phospholipid syndrome and connective tissue disorder. Also low socio-economic status have been identified by some authors as a risk factor. 85-86

**AETIOLOGY**

The exact aetiology of pre-eclampsia remains unknown. Different theories have been proposed, but none has explained all the pathological features of the disease. These theories include increased vascular reactivity, genetic and immunologic susceptibility, disseminated intravascular coagulation, imbalance of prostanoids production, abnormal trophoblastic invasion and excessive production of free radicals and lipid peroxidases. 27 However, it is believed that there is a genetic predisposition which leads to a failure of the usual tolerance between the fetal allograft and the maternal decidua. This immunological intolerance leads to a failure of the second wave of cytotrophoblastic invasion of the maternal myometrial spiral arteries. 27 As a result the myometrial spiral arteries remain muscular, undilated and responsive to vasomotor influences. The utero-placental blood flow is therefore reduced. The resulting hypoxia leads to oxidative stress with the release of circulating factors from the placenta bed. The precise nature of these circulating
factors remain speculative but are believed to include lipid peroxidation products, reactive oxygen species (superoxide anion and hydroxyl radicals), cytokines (tumor necrosis factor-α and interleukin-6), placental syncytiotrophoblast membrane, and vascular endothelial growth factors. All these circulating factors lead to widespread vascular endothelial damage. Vascular endothelial damage remain the central piece of the pathogenesis of pre-eclampsia, with the multi-systemic manifestation of the disease arising from this singular event. The endothelium is important in the modulation of vascular tone. Damaged endothelium leads to a reduction in the production of prostacycline and nitric oxide which are major vessel dilators while the production of thromboxane A2 and endothelium 1, which are vasoconstrictors, are increased.

The endothelial vascular damage leads to the multisystemic manifestation of the disease. The systemic vasoconstriction due to increased production of vasoconstrictors leads to systemic hypertension. Thrombocytopenia and coagulopathy occurs as a result of platelet aggregation and fibrin mesh-work formation on the damaged endothelium. Altered vascular permeability leads to peripheral and pulmonary oedema. In the kidneys, the endothelial damage leads to proteinuria and acute renal failure. In the central nervous system, the increased vascular resistance and vasoconstriction leads to hypoxia with
associated oedema which causes the seizure, cerebrovascular accident, cortical blindness and retinal detachment. At the placenta bed, the reduction in the blood supply due to the increased vascular resistance lead to fetal growth restriction, hypoxia and abruption placenta.

**SCREENING**

Many screening tests for predicting pre-eclampsia based on dysfunction of placental perfusion, vascular resistance, endocrinology and the fetoplacental units have been described. A systematic review conducted by the World Health Organisation (WHO) to evaluate these screening methods found the majority of them to have low predictive potential and thus not suitable for use in routine clinical practice.\textsuperscript{68} Antenatal screening therefore consists predominantly of detection of a raised blood pressure and proteinuria. Once detected, treatment of pre-eclampsia has remained delivery of the fetus and placenta for the last century. While blood pressure is measured using mercury sphygmomanometer which relies on detecting Korotkoff sounds and more recently with the use of automated blood pressure measuring equipment, which is fraught with errors,\textsuperscript{54} several advancements have been made in detection of proteinuria.
MEASUREMENT OF PROTEINURIA

There have been several advancements in the detection of proteinuria since the nineteenth century. It was in 1827 that Bright boiled a teaspoon of urine and discovered “albuminous urine” in patients with oedema and related this to severe and protracted disease of the kidneys. In 1843, the Obstetrician John Lever separated the proteinuria of pregnant women in whom hypertension was developing from that of “Morbus Brightii” (Bright’s disease). Since this discovery, proteinuria has been used to define pre-eclampsia and classify disease severity. Patterns of proteinuria have also been investigated to distinguish pre-eclampsia from other proteinuria diseases.

Proteinuria is defined as the excretion of 300mg or more of protein every 24 hours. If 24-hour urine samples are not available, proteinuria is defined as a protein concentration of 300mg/I or more (≥ 1 + on dipstick) in two clean catch midstream or catheter specimens of urine collected 4 hours or more apart or a spot protein to creatinine ratio of 30mg/mmol or more (Sibai et al, 2005). In order to detect pre-eclampsia, blood pressure measurement and dipstick analysis of urine for protein have become a part of routine antenatal screening.

Traditionally a quantitative 24-hour total urinary protein excretion has been used to qualify proteinuria. New development in proteinuria
assessment have included the use of urinary albumin measurements. While small amounts of albumin can be detected in the urine of a healthy population. Microalbuminuria (MA) has been used to refer to a range of urinary albumin excretion that is above the reference ranges but below amounts referred to as significant proteinuria (20-200mg/l). In the non-pregnant population microalbumin has been extensively studied. It has been used as a marker to predict an increase risk of cardiovascular and renal disease in the general population, in type 1 and 2 diabetics and in patients with essential hypertension.\textsuperscript{75,77}

In the pregnant population, there is limited literature regarding microalbuminuria. It has been used as a clinical tool to predict pre-eclampsia and as an early predictor of hypertensive complications and perinatal outcomes. Waugh et al,\textsuperscript{37} have suggested that microalbuminuria may correlate better with other clinical measurements of disease severity as it may more accurately reflect the glomerular dysfunction associated with the glomerular endotheliosis of pre-eclampsia. Microalbuminuria dipsticks have also been shown to be a better screening test for clinically significant proteinuria.\textsuperscript{37,46}

**RENAL CHANGES IN NORMAL PREGNANCY**

In normal pregnancy, Glomerular filtration rate and effective renal plasma flow increase by approximately 50%. Clinically, GFR is determined by measuring creatinine clearance (CC). Creatinine clearance
reliably correlates with GFR provided that a complete urine collection is obtained during an accurately timed period. Creatinine clearance is significantly increased by 4 weeks gestation. In the last four weeks of pregnancy CC reduces by 15-20%. In pregnancy CC may be increased to values of 150-200ml/min. These renal haemodynamics changes result in greater quantities of colloids and solute passing by the glomerular barrier per unit time.

In addition there are changes in glomerular permeability and altered tubular reabsorption of filtered proteins that may result in increased excretion of protein. Thus it is normal in pregnant women for total protein excretion (TPE) and urinary albumin excretion (UAE) to be significantly elevated after 20 week of gestation. Currently, the accepted upper limits of normal for protein excretion in pregnancy are 300mg/24hours for total protein excretion and 30mg/24hours for urinary microalbumin. Kuo et al, have suggested that a threshold for pregnancy should be lowered to 200mg/24hours for Total Protein Excretion(99th centile at 17-20 weeks gestation to be 300mg/24hours and at 33-36 weeks to be 200mg/24 hours) but it is 300mg threshold that remains in clinical use.

**RENAL CHANGES IN PRE-ECLAMPSIA**

In pre-eclampsia there is a reduction of both GFR and ERPF by 30–40% compared with normal pregnancy. It is postulated that the basis
for the hypofiltration is largely secondary to structural changes in the glomerulus as opposed to renal vasoconstriction with a depression in renal plasma flow. Rarely, prolonged renal hypoperfusion with resulting acute tubular necrosis can occur in severe pre-eclampsia.

Proteinuria may rarely precede hypertension but usually accompanies or follow it, after pregnancy is terminated, proteinuria commonly disappears within 3-8 weeks, but occasionally persist for months. Pre-eclampsia is the leading cause of nephritic syndrome during pregnancy. Protein excretion may vary from less than a gram to 8 to 10 g per day. The urinary sediment is usually bland with red blood cells and cellular cast being rare.

In pre-eclampsia, glomeruli undergo structural changes with endothelial vacuolization and hypertrophy of the cytoplasmic organelles defined as glomerular endotheliosis. Loss of both size and charge selectivity of the glomerular barrier contribute to the development of albuminuria. The proteinuria of pre-eclampsia is thus considered to be non-selective.

Recently, Garovic et al. demonstrated the presence of 4 podocyte markers (Podocin, Pocalyxin, Synaptopodin and nephrin) in patients with pre-eclampsia at the time of delivery. Podocyturia (i.e. urinary excretion of Podocytes) may contribute to proteinuria in pre-eclampsia and may
indicate loss of Podocytes from the glomerulus leading to disruption of
the glomerular filtrate barrier and subsequent proteinuria.

**DIPSTICK URINALYSIS**

Proteinuria is assessed most appropriately by the biochemical
quantitative measurement of total protein excretion over a 24-hour period.
This is an impractical screening test. The most commonly employed
screening method for proteinuria antenatally is a semi-quantitative
dipstick urinalysis.\textsuperscript{79}

Several studies have questioned the value of dipstick urinalysis.
Kuo et al,\textsuperscript{70} compared the dipstick diagnosis of significant proteinuria in
24-hour collections with dipstick urinalysis in 68 hypertensive pregnant
women admitted to hospital with 0.3g/l proteinuria on urinalysis. They
found a wide range of total protein values at a urine score of 1+ on
dipstick urinalysis. They reported sensitivity of 60%, specificity of
82%, PPV of 84%, NPV of 81%, FPR of 18%, FNR of 40%.

Meyer et al,\textsuperscript{91} retrospectively reviewed case records of 300
hypertensive women. They reported that 60% of women with a negative
or trace dipstick result had significant proteinuria defined as $\geq 0.3g$
protein/24hours and a significant false positive rate of 26% with a 1+
dipstick result, with sensitivity of 40%, specificity of 74%, PPV of
78%, NPV of 80%.
Brown et al, \textsuperscript{57} compared ward urinalysis for protein obtained on a midstream sample before and after 24-hour urine collection and compared this with the 24-hour urine protein excretion. Urinalysis was also performed on a mixed aliquot of each 24-hour urine sample. The positive predictive value for urinalysis ranged from 38\% (pre collection) to 60\% (for test on 24 hour aliquot). Negative predictive values ranged from 86\% to 88\% respectively. The false negative rate (FNR) ranged between 8-18\% with a very high false positive rate (FPR) of 67\%.

Waugh et al, \textsuperscript{31} found that dipstick urinalysis has a significant false negative rate regardless of the type of assessment with Sensitivity of 22.5\%(95\% CI 15.8-30.3\%), specificity of 98.3\%(95\% CI 90.9-99.9\%), PPV of 96.9\%(95\% CI 83.9-99.9\%), NPV of 35.2\%(95\% CI 27.9-43.0\%). FPR of 1.7\% and FNR of 67.5\%.

These studies show that random semi-quantitative dipstick analysis in the diagnosis of proteinuria in pregnancy is imprecise and its value is questionable. False positive results may subject patients to the inconvenience of over investigation and unnecessary interventions, while false negative results may jeopardize the health of the woman and her fetus.
PROTEIN: CREATININE RATIOS IN SPOT URINE SAMPLES

The gold standard for determining protein excretion is the 24 hour urine collection. The need for a 24 hour collection is due to the variation in protein excretion during the day. Factors that may contribute to this variation include variation in water intake and excretion, rate of diuresis, exercise, recumbency and diet.\textsuperscript{24}

The major problem with the 24 hour protein collection is that it is often impractical in the outpatient setting with problems of incomplete collection. In order to overcome this, the spot protein to creatinine ratio has been proposed. During the day urinary protein and creatinine excretion rates are fairly constant provided the glomerular filtration rate is constant. Hence, the concentrations of urinary protein and creatinine in a single voided urine sample would reflect the cumulative excretion during the day since the ratio of two stable rates would cancel out the time factor.\textsuperscript{69}

Recent studies have suggested a strong correlation between the protein/creatinine ratio and 24 hour urine protein level in women with pre-eclampsia.\textsuperscript{22,47} Eigbefoh et al\textsuperscript{22} measured the protein:creatinine ratio in 86 patients with hypertensive disorders of pregnancy. They found a close correlation between the protein/creatinine ratio in random urine samples and the 24 hour urine protein in patient with pre-eclampsia with
sensitivity of 92%, specificity of 86%, PPV of 83%, NPV of 93%, FPR of 14%, FNR of 8% and accuracy of 88%.

Besides showing a significant correlation between 24-hour urine protein and the protein:creatinine ratio, Neithardt et al. found in addition that the protein:creatinine ratio appears to predict trends in protein excretion over time ($r=0.84; p<.001$), sensitivity, specificity, PPV, NPV of 91.2%, 87.8%, 94.4%, and 96.8% respectively.

Other studies have found contradictory results. Durnwadd et al. found a poor correlation between the protein/creatinine ratio in 220 women with suspected pre-eclampsia (sensitivity 64.8%, specificity 55.8%, PPV 85.5%, NPV 47.5%, FNR 35.2%, $r(2)=0.41$).

A systematic review by Price et al. concluded that there was sufficient data to demonstrate a strong correlation between the protein:creatinine ratio in a random urine sample and 24 hour protein excretion (sensitivities and specificities ranged between 69% and 96% and 41% and 97% respectively, whereas the positive and negative predictive values ranged between 46% and 95% and 45% and 98% respectively. The positive and negative likelihood ratios ranged between 1.8 and 16.5 and 0.06 and 0.35 respectively). They also found that protein:creatinine ratio in a random urine sample might be used to rule out significant proteinuria as defined by a 24 hour urine excretion measurement.
To increase the applicability of the use of the protein:creatinine ratio in clinical practice semi-quantitative protein: creatinine ratio dipsticks have been developed. Roy et al\textsuperscript{28} compared this with the use of visual dipsticks and 24hour total protein measurement as the gold standard. They found the sensitivity (94.5\% vs 82\%) and specificity (95.7\% vs 81\%) of the protein: creatinine ratio dipsticks to be superior to visual dipsticks urinalysis for the prediction of 300mg protein/24 hours at the 1+ threshold.

**MICROALBUMINURIA**

The term microalbuminuria was first used by Viberti et al\textsuperscript{31} in 1981 to predict development of overt proteinuria in diabetic patients and to screen and monitor incipient nephropathy in this patient. More recently it has been found to be an independent predictor of cardiovascular disease in patients with diabetes, hypertension and in the general population.\textsuperscript{52,73,76} It has also been suggested as a marker of endothelial dysfunction.\textsuperscript{73} These findings have led to an increased interest in the role of microalbuminuria in hypertensive disorder of pregnancy.

Microalbuminuria is defined as a urinary excretion rate of albumin between 20-200µg/min or between 30-300mg/24hours or between 20-200mg/l or between 24-200mg/g creatinine. Traditionally this has been measured using 24 hour urine collection. The definition has been
expanded to include spot urinary microalbumin to creatinine ratio (UAC) of 30 to 300mg/g or 3.4-33.9mg/mmol.\textsuperscript{76}

When using the UAC, various factors affecting albumin and creatinine excretion need to be taken into account. Factors affecting albumin include blood pressure, time of day, fasting, salt intake and volume status.\textsuperscript{71}

During the 1990’s, the most sensitive strips for detection of albuminuria had thresholds for detection of 20mg/l. Thus a lower limit of 30mg/day was chosen for the definition of microalbuminuria as the average daily urine output of 1.5 litres was multiplied by 20mg/l. The upper limit of 300mg/day was chosen as the sensitivity of the older dipsticks for albumin was 100 to 300mg/l.\textsuperscript{76}

Recent studies have demonstrated that subjects with even slight increases in urinary albumin excretion in the normal range have an increased risk for development of cardiovascular morbidity and mortality.\textsuperscript{17} This suggests that the limits chosen for microalbuminuria are arbitrary and the best cut offs still need to be identified.\textsuperscript{76}

**PATHOPHYSIOLOGY OF MICROALBUMINURIA**

Microalbuminuria (MA) appears to be more a marker of vascular disease than a pathogenic factor. Factors known to influence the development of microalbuminuria include an increased body mass index (BMI), hypertension, endothelial dysfunction, a decrease in high density
lipoprotein levels, insulin resistance, smoking, salt sensitivity, increasing age and a DD ACE – genotype.\textsuperscript{71,73}

Patients with microalbuminuria have an elevated transcapillary escape rate of albumin, and usually the presence of one or more of the above risk factors. The mechanism of vascular injury differs among diabetic and hypertensive populations. In hypertensive patients with microalbuminuria, increases in microvascular pressure results in endothelial damage, leading to generalized vascular leakiness. Excess protein is deposited in the extracellular matrix, resulting in the capillary basement membrane becoming sclerosed. This response is mediated through various stimuli such as, complement activation, macrophages, neutrophils, and endothelial stimulation from other inflammatory insults.\textsuperscript{71,73}

In diabetic patients, the glycated state of albumin transforms it into an antigenic molecule that is associated with generation of free oxygen radicals that causes direct injury to the glomerular membrane. This impairs glomerular filtration of proteins resulting in increased albumin excretion.\textsuperscript{71,82} The link between diabetic and non-diabetic microalbuminuria may be impaired insulin resistance, leading to an increased amount of glycated albumin.
MICROALBUMINURIA IN PREGNANCY

Recently there has been interest in the measurement of microalbumin in the urine of pregnant women. Proteinuria in pregnancy is due to selective glomerular filtration and non-selective (proximal tubule) reabsorption. In non-pregnant women there is an albumin filtration of 500mg – 600mg/day. During pregnancy proteinuria gradually increases with levels of 5mg/100mls in the first and second trimesters and 10mg/100ml in the third trimester. Levels in the third trimester may reach 300mg/ml in normal pregnancy.

MICROALBUMINURIA AND HYPERTENSIVE DISORDERS OF PREGNANCY

It has been suggested that a phase of microalbuminuria may precede overt proteinuria in pre-eclampsia. There has been mixed results in the literature on the usefulness of microalbuminuria as an early predictor of pre-eclampsia.

Lopez-Espinoza et al found no evidence that gross proteinuria detected in patients with pre-eclampsia was preceded by a gradual increase in microalbuminuria and Konstantin-Hansen et al concluded that microalbuminuria could not be used to predict pre-eclampsia in low risk pregnant woman.

Nakamura et al in a study of 199 normotensive pregnant women at 20 and 30 weeks of gestation, found the fasting urinary albumin to
creatinine ratio to be significantly higher in women destined to develop pregnancy induced hypertension. Using a cut off value of more than 16mg/g as a positive test result, the negative predictive value was 94% for 20weeks and 96% for 30weeks gestation, whereas the PPV were 50% and 43% respectively and thus they concluded that this was a useful screening tool for predicting pregnancy induced hypertension.

Das et al\textsuperscript{93} concluded that microalbuminuria was a significant risk factor for prediction of pre-eclampsia. Using $\geq 20\mu$/ml of urinary albumin as a positive test, they found a sensitivity of 68% and specificity of 92%, PPV of 56% and NPV of 94%.

Microalbuminuria dipsticks have also been used to detect clinically significant proteinuria.\textsuperscript{34-35,46} Higby et al\textsuperscript{46} compared two screening tests of microalbuminuria, namely the micro-bumintest and multistix 10SG with a 24hour quantitative urinary protein measurement. They found the micro-bumintest to have good sensitivity (87%), specificity (99%), PPV (81%) and NPV (99%) compared to the multistix 10SG which has a lower sensitivity (36%), specificity (97%), PPV (68%) and NPV (88%).

Besides being used as a predictor of pre-eclampsia it has also been suggested that microalbuminuria may correlate better with other clinical measurements of disease severity as it may more accurately reflect the glomerular dysfunction associated with the glomerular endotheliosis of pre-eclampsia.\textsuperscript{35}
Microalbuminuria dipsticks compared to the traditional visual urinary dipsticks have also been shown to be a better screening test for clinically significant proteinuria. Various semi-quantitative dipstick tests have been used for detection of microalbuminuria. In order to allow routine testing of the antenatal population for microalbuminuria, quantitative and semi-quantitative point of care urinalysers have been developed. However, these facilities are not currently used in our environment because of cost and availability.
SIGNIFICANT PROTEINURIA

Twenty-four hour urinary protein which is the gold standard is significant when the total protein excretion of 300mg or more in 24 hours urine is present and severe proteinuria is diagnosed when total urinary protein is ≥ 3g/24hours. However, the limitations with this is that it is cumbersome, is expensive, there is delay in making diagnosis and interventions, sample collection is difficult and inaccurate, above all it requires admission.

In visual dipstick urinary strips, two clean–catch midstream or catheter specimens of urine collected 4hours or more apart is used and is significant when there is proteinuria of 2+ or more i.e (1g/L) or 1+ (0.3g/L) if specific gravity is < 1.030 and PH < 8. The advantage of visual dipstick is that it is handy, cheap, fast, easy to administer, does not need special training, however it has poor sensitivity, specificity, negative predictive value and positive predictive value.33

The protein-creatinine ratio cut off ≥30mg/mmol has been used and it correlates with 24hour urinary protein in term of sensitivity, specificity, negative predictive value and positive predictive value, and should replace visual dipstick in clinical practise, however it is expensive and requires training.22
Microalbumin cut off of 30mg/dL has been used. It correlates well with 24-hour urine protein however the strips are not readily available, is more expensive than visual dipsticks.\textsuperscript{76}

Spot urinary microalbumin:creatinine ratio cut off of >30mg/g (3.4mg/mmol) is considered as positive for significant proteinuria and correlates well with 24-hour urine protein with sensitivity of 94% and specificity of 98%. It also has good positive predictive value and negative predictive value and is a suitable substitute to visual dipsticks however is more expensive than visual dipstick and the technology is not yet embraced and few studies have been done to validate its benefits.\textsuperscript{76}
JUSTIFICATION FOR THE STUDY

Pre-eclampsia and eclampsia are major causes of maternal and perinatal morbidity and mortality and accounts for over 100,000 of over half a million deaths worldwide and now a leading cause of maternal mortality in Irrua Specialist Teaching Hospital, Irrua (my centre).

Early detection and prompt management of patients with proteinuria is beneficial to the patient and fetus and will help avert morbidity and mortality.

The gold standard for measuring proteinuria is 24 hours urine sample this is because of variation in protein excretion during the day, which is affected by factors such as water intake and excretion rate of diuresis, exercise, recumbency and diet. However the major problem with 24 hour protein collection is that it is often impractical in the outpatient setting with problems of incomplete collection. Also this results in delay in making diagnosis and treatment which may increase maternal and perinatal morbidity and mortality. Besides, the collection is cumbersome, often incomplete and difficult to administer, most time requiring admission, increase cost with possible prolonged hospital stay, hence there is need to find a method that is shorter, quick, easy to administer and correlates well with 24 hour urinary protein excretion.

Unfortunately, the most widely used screening test for proteinuria, the dipstick test has been fraught with error and correlates poorly with 24
hour urinary protein excretion. Hence there remains therefore the need for a reliable semi-quantitative measurement of urinary protein excretion that will be quick, easy to administer and also correlates well with 24-hour urinary protein excretion.

Microalbuminuria has been found to fill this vacuum, it is a predictor of pre-eclampsia, marker of disease severity, more accurately reflect glomerular dysfunction associated with glomerular endotheliosis of pre-eclampsia and better screening test for clinically significant proteinuria. It was first used by Viberti et al in 1981 to predict development of overt proteinuria in diabetic patients and to screen and monitor incipient nephropathy in this patient. More recently it has been found to be an independent predictor of cardiovascular disease in patients with diabetes, hypertension and in general population.

It has also been suggested as a marker of endothelial dysfunction which is the main pathology in pre-eclampsia and eclampsia. This findings have led to an increased interest in the role of microalbuminuria in hypertensive disorders of pregnancy. It also appears to be more a marker of vascular disease than a pathogenic factor. It is also suggested to be a good predictor of pre-eclampsia since there may be a phase of microalbuminuria preceding overt proteinuria in pre-eclampsia.

Recently microalbuminuria dipsticks have been used to detect clinically significant proteinuria, using albumin cut-off of 30mg/l, it has
been found to have a good sensitivity, specificity, positive predictive value and negative predictive value and correlates better with other clinically measurements of disease severity as it may more accurately reflect the glomerular dysfunction associated with the glomerular endotheliosis of pre-eclampsia.\textsuperscript{35}

Much more accurate is the use of spot urinary microalbumin to creatinine ration (UAC) of 30-300mg/g or 3.4-33.9mg/mmol. Creatinine excretion rates are fairly constant provided the glomerular filtration rate (measured by creatinine clearance) is constant. Thus a ratio of the concentrations of urinary protein and creatinine in a single voided urine sample would reflect the cumulative excretion during the day since the ratio of two stable rates would cancel out the time factor. Recent studies have suggested a very strong correlation between the UAC ratio and 24 hour urine protein in women with pre-eclampsia,\textsuperscript{22,27} besides this correlation, UAC ratio appears to predict trends in protein excretion over time. At albumin concentration >40mg/L the accuracy of UAC ratio in measuring significant proteinuria, the 95% limits of agreement are broader.

Thus a spot urinary microalbumin to creatinine ratio cut off of >30mg/g (3.4mg/mmol) is considered as positive for significant proteinuria and correlates well with 24hours urine protein with sensitivity of 94%, specificity of 98% as against microalbuminuria alone which has
sensitivity of 58% and specificity of 83%. Furthermore, the urinary microalbumin to creatinine ratio has a good negative predictive value and a result of <3.4mg/mmol rules out significant proteinuria and avoids unnecessary investigations in pregnancy. These improved sensitivity, specificity & NPV of (UAC) over the visual dipstick suggests that it may be a suitable substitute for visual dipstick in clinical practice for it has the potential to improve accuracy of screening for proteinuria and enhancing safety by preventing incorrect diagnosis and unnecessary investigations. However, further research is required to determine its full impact and cost effectiveness in the clinical setting. Above all, the use of 24 hour, 2 hour and 8 hours urinary protein in the determination of severity of pre-eclampsia has been validated in our clinical setting but little is known about the utilization of spot microalbumin; creatinine ratio in determining the severity of pre-eclampsia.
AIMS AND OBJECTIVE

The aim of this study is to determine the accuracy and diagnostic value of spot urinary microalbumin: creatinine ratio in single voided urine samples for quantification of proteinuria compared to 24 hour urine protein collection in patients with pre-eclampsia.

The specific objectives are:

1. Compare the accuracy of spot microalbumin dipsticks and microalbumin: creatinine ratio
2. Compare accuracy of spot microalbumin dipstick to 24 hour urinary protein.
LIMITATION

1. Quantitation of one of the test is based on reading colours which could be subjective.

2. Cost – Is more expensive than traditional visual dipsticks.

3. Poor correlations when protein is <1mg/dL or >128mg/dl in 24 hour urine protein.
MATERIALS AND METHOD

Study Design: Cross-sectional study

Setting: Antenatal Clinics, Antenatal and Labour Wards, Accident and Emergency Unit of Irrua Specialist Teaching Hospital, Irrua, Edo State. It is a tertiary hospital and a referral Centre for parts of Edo, Kogi, Ondo and Delta States. The hospital has 42 gynaecological and 48 Obstetrics beds and undertakes an average of 1,200 deliveries annually.

SAMPLE SIZE

The sample size was calculated by a statistical formula based on the prevalence of 5% for pre-eclampsia and a confidence level set at 95% with an error margin of 0.05.\(^8\)

\[
N = \frac{PQ}{(E/1.96)^2}
\]

Where:

\(N\) is the sample size

1.96 is a known constant (Standard normal deviation corresponding to 95% confidence level).

\(P\) is the maximum known prevalence of the disease

\(Q\) is \(1 - P\) (proportion of the persons free from the disease)

\(E\) is the error margin

Using the maximum reported incidence of 5% and error margin of 0.05.

\[
N = \frac{0.05 \times 0.94}{(0.05/1.96)^2} = 73
\]
Attrition of 10% was added; hence sample size became 80.

METHODS

Eighty consecutive pregnant women with pregnancy induced hypertension at gestational age >20 weeks scheduled for a 24-hour urine sample collection was recruited into the study. The patients were on modified bed rest in the hospital.

Exclusion criteria include women who decline, women with chronic renal disease, eclampsia, hydatidiform mole, connective tissue diseases, diabetes mellitus, pathological vaginal discharge, urinary tract infections and prior vulval or vaginal cleansing with antiseptics or skin cleansers like chlorhexidine and patients requiring delivery before completion of urine sample.

Diagnosis of hypertension was based on two consecutive measurements of diastolic blood pressure of 90mmHg 4 hours or more apart, one measurements of diastolic pressure of 110mmHg or more or a rise of 30mmHg or 15mmHg above normal pre-pregnancy systolic or diastolic blood pressures respectively, after 20 week of pregnancy taken in the sitting position or left lateral position using an appropriate sized cuff and Korotkoff Phase V (disappearance of sound) as the diastolic pressure.

Total urine collection time was 24 hours. Inpatients had the assistance of the nursing staff for collection. Each container was labelled
with the patient's name, number of the container and collection time. A microalbumin/creatinine ratio and a urine dipstick test for protein was done on urine voided after rising (physical activity can increase the elimination of albumin especially if a random urine sample is used) within the 24 hours.

**Urine Dipstick Test:** The dipstick tests were done using the multistix 10SG Urinalysis strip manufactured by Bayer Pharmaceuticals. Significant proteinuria was 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 1.030 and pH less than 8.23

**24 Hour Urine Protein:** The urine was stirred to ensure homogeneity and a 6ml 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 measured the shift in the absorption that occurred when the pyrogallol red-molybdate complex in the reagent binds basic amino acid groups of protein in the test sample (mg/dl). Each sample was run in duplicate and the mean value used in the calculations. Samples were run with low and high controls. This assay was compared with other similar commercially available reagents. Studies have shown correlation coefficient of 0.997 for samples containing 1mg/dL to 128mg/dL. For samples with significant proteinuria that exceeds this
value, the urine was diluted 1:10 with deionized water. Significant proteinuria was defined by one 24-hours urine collection with total protein excretion of 300mg and more.

**Microalbuminuria Test:** This was done using Micral Test (R) (An Accu-CHEK Product). The test strip was put into the urine such that the fluid level was just between the two black bars and not touching the side of the vessel in the process. The test strip was withdrawn after 5 seconds and read after 1 minute by comparing the colour change above the inscription “Micral” with the colour scale on the test strip container label. Comparism of reaction colour with the colour scale was possible for another 5 minutes.

*The test strip contains per cm²:* Monoclonal antibodies against human albumin (immunoglobulin c1) labeled with colloidal gold: 6µg, fixed albumin: 9.5µg. The test principle was based on the immunological detection of human albumin by means of soluble antibody – gold – conjugate. Excess conjugate was retained in a separation zone containing immobilized human albumin. Cross reactions from other human protein from studies was found to be < 0.5%.89

**Creatinine:** The urinary creatinine was done using the modified Jaffe’s 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, creatinine alkaline picrate, which can be photometrically measured. The serum creatinine was determined by using the same assay with 300µL of serum. Estimation of the creatinine clearance was calculated by using the following formula:

\[ \text{Creatinine Clearance} = \frac{\text{Urine creatinine (mg/dL)} \times \text{Volume (mL)}}{\text{Serum creatinine (mg/dL)} \times \text{Time (min)}} \]

The tests 24-hour urine protein and creatinine estimation was performed by a biochemist working in the laboratory of the hospital who was co-opted into the study, while the other tests was done by Doctors specially trained to carry out the investigations and interprete the results. For each patient, information on the age, parity and gestational age and other risk factors was obtained. The results of the tests was recorded in a structured data sheet (Appendix 1).

Based on the results, the sensitivity, specificity, false positive and false negative rates, positive predictive value, negative predictive value and accuracy was determined when the spot microalbuminuria/creatinine ratio was compared with dipstick protein estimation and 24 hour urine protein estimation.

**DATA ANALYSIS**

Data was analysed using SPSS 16 statistical package. Tables was used to represent variables and results. Chi – square analysis was used for comparing proportions of categorical variables while the student’s ‘t’ test
was used for comparing means where applicable. P – value less than 0.05 was taken as significant.

**MEASURES OF TEST VALIDITY AND RELIABILITY**

Number of true positive samples = $TP$

Number of true negative samples = $TN$

Number of false positive samples = $FP$

Number of false negative samples = $FN$

**Sensitivity** – Percentage of women with significant proteinuria correctly identified by the test = $\frac{TP}{(TP + FN)} \times 100/1$

**Specificity** – Percentage of women without significant proteinuria correctly identified by the test = $\frac{TN}{(TN + FP)} \times 100/1$

**Positive Predictive Value** – Probability that a woman with a positive result has significant proteinuria = $\frac{TP}{(TP + FP)} \times 100/1$

**Negative Predictive Value**-Probability that a woman with a negative result do not have significant proteinuria = $\frac{TN}{(TN+FN)} \times 100/1$

**False Positive Rate** – Percentage of all women with positive results who do not have Significant proteinuria = $\frac{FP}{(TP + FP)} \times 100/1$

**False Negative Rate** – Percentage of all women with negative results who actually have significant proteinuria = $\frac{FN}{(TN + FN)} \times 100/1$

**ACCURACY**- Number of true positive and true negative results over the sample size = $TP + TN/N$

35
ETHICAL CONSIDERATIONS

Approval for the study was obtained from the ethical committee of the Irrua Specialist Teaching Hospital. Ethical considerations in this study was based on the general ethical principles as applicable to human subjects. These were respect for persons, beneficence, non-malficience and justice.

1. **Respect for Persons:** Patients were recruited into the study after adequate information was provided and informed consent was obtained. They were not coerced or induced to participate and their right to participate or to withdraw from the study was respected.

2. **Beneficence:** Ethical obligation to maximize benefits and minimize harm or wrong. Blood samples were collected using aseptic technique and with due competence. Patients were not made to bear any part of the cost of investigation.

3. **Non-malficience:** No harm done to subject. Strict adherence to principles 1 and 2 above ensured that no harm was done to the patients in the study.

4. **Justice:** Patients were treated equally. Refusal to participate in the study did not alter the management of patients.

In addition, data was not manipulated to suit presumed results.
# RESULTS

## TABLE I. SOCIODEMOGRAPHIC VARIABLES

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<th>Frequency</th>
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### TABLE IIa. VISUAL DIPSTICK VS 24HOUR URINARY PROTEIN VALUE

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<tr>
<th>TESTS</th>
<th>24HOUR URINARY PROTEIN VALUE</th>
<th>Total</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>VISUAL DIPSTICK</td>
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<td>TRACE</td>
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<tr>
<td>1+</td>
<td>23</td>
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<tr>
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<tr>
<td><strong>Total</strong></td>
<td>61</td>
<td>19</td>
</tr>
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P = 0.03

### TABLE IIb. POSITIVE VISUAL DIPSTICK (1+ - 4+) VS 24HOUR URINARY PROTEIN VALUE VALIDITY

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<th>24HOUR URINARY PROTEIN VALUE</th>
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<tr>
<td>FN</td>
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</tbody>
</table>

Sensitivity: 72.1%
Specificity: 68.4%
Positive predictive value: 88.0%
Negative predictive value: 43.3%
False positive rate: 31.6%
False negative rate: 27.9%
Accuracy: 71.3%
TABLE IIIa. MICROALBUMIN DIPSTICK VS 24HOUR URINARY PROTEIN VALUE

<table>
<thead>
<tr>
<th>TESTS</th>
<th>24HOUR URINARY PROTEIN VALUE</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POSITIVE</td>
<td>NEGATIVE</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>MICROALBUMIN DIPSTICK (mg/L)</td>
<td>NEGATIVE</td>
<td>1</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>20mg/L</td>
<td>5</td>
<td>9</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>50mg/L</td>
<td>35</td>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>100mg/L</td>
<td>18</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>&gt;100mg/L</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>61</td>
<td>19</td>
<td>80</td>
</tr>
</tbody>
</table>

P=0.00

TABLE IIIb. POSITIVE MICROALBUMIN DIPSTICK (20mg/l - >100mg/l) VS 24HOUR URINARY PROTEIN VALUE

<table>
<thead>
<tr>
<th>TESTS</th>
<th>24HOUR URINARY PROTEIN VALUE</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POSITIVE</td>
<td>NEGATIVE</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>MICROALBUMIN DIPSTICK (mg/L)</td>
<td>POSITIVE</td>
<td>TP</td>
<td>FP</td>
<td>TP+FP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60</td>
<td>12</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>NEGATIVE</td>
<td>FN</td>
<td>TN</td>
<td>FN+TN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>7</td>
<td>8</td>
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<tr>
<td></td>
<td>Total</td>
<td>TP+FN</td>
<td>FP+TN</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td></td>
<td>61</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity 98.7%
Specificity 36.8%
Positive predictive value 83.3%
Negative predictive value 87.5%
False positive rate 63.2%
False negative rate 1.6%
Accuracy 83.8%
TABLE IV: MICROALBUMIN/CREATININE RATIO VS 24HOUR URINARY PROTEIN VALUE

<table>
<thead>
<tr>
<th>TESTS</th>
<th>24HOUR URINARY PROTEIN VALUE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POSITIVE</td>
<td>NEGATIVE</td>
<td>Total</td>
</tr>
<tr>
<td>MICROALBUMIN/CREATININE RATIO</td>
<td>TP</td>
<td>FP</td>
<td>TP+FP</td>
</tr>
<tr>
<td>POSITIVE</td>
<td>58</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>NEGATIVE</td>
<td>3</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>19</td>
<td>80</td>
</tr>
</tbody>
</table>

P=0.00

Sensitivity 95.1%
Specificity 89.5%
Positive predictive value 96.7%
Negative predictive value 85.0%
False positive rate 10.5%
False negative rate 4.9%
Accuracy 93.6%
### TABLE V: MEASURE OF RELIABILITY AND VALIDITY OF VARIOUS TESTS

<table>
<thead>
<tr>
<th></th>
<th>VISUAL DIPSTICK</th>
<th>MICROALBUMIN DIPSTICK</th>
<th>MICROALBUMIN/CREATININE RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>72.1</td>
<td>98.4</td>
<td>95.1</td>
</tr>
<tr>
<td>Specificity</td>
<td>68.4</td>
<td>36.4</td>
<td>89.5</td>
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<tr>
<td>Positive predictive value</td>
<td>88.0</td>
<td>83.3</td>
<td>96.7</td>
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<tr>
<td>Negative predictive value</td>
<td>43.3</td>
<td>87.5</td>
<td>85</td>
</tr>
<tr>
<td>False positive rate</td>
<td>31.6</td>
<td>63.2</td>
<td>10.5</td>
</tr>
<tr>
<td>False negative rate</td>
<td>27.9</td>
<td>1.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Accuracy</td>
<td>71.3</td>
<td>83.8</td>
<td>93.8</td>
</tr>
</tbody>
</table>

### TABLE VI: RELIABILITY AND VALIDITY OF VARIOUS TESTS AT DIFFERENT VALUES VS 24HOUR URINARY PROTEIN

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity %</th>
<th>Specificity %</th>
<th>PPV %</th>
<th>NPV %</th>
<th>FPR %</th>
<th>FNR %</th>
<th>Accuracy %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VISUAL DIPSTICK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual dipstick at trace</td>
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<td>68.4</td>
<td>88</td>
<td>43.3</td>
<td>31.6</td>
<td>27.9</td>
<td>71.3</td>
</tr>
<tr>
<td>Visual dipstick at 1+</td>
<td>76.5</td>
<td>46.2</td>
<td>65.0</td>
<td>60.0</td>
<td>53.9</td>
<td>23.5</td>
<td>63.3</td>
</tr>
<tr>
<td>Visual dipstick at 2+</td>
<td>57.5</td>
<td>72.2</td>
<td>82.1</td>
<td>43.3</td>
<td>27.8</td>
<td>42.5</td>
<td>62.1</td>
</tr>
<tr>
<td>Visual dipstick at 3+</td>
<td>24.5</td>
<td>94.7</td>
<td>92.3</td>
<td>31</td>
<td>5.3</td>
<td>75.5</td>
<td>43.1</td>
</tr>
<tr>
<td>Visual dipstick at 4+</td>
<td>8.6</td>
<td>100</td>
<td>6.9</td>
<td>26.4</td>
<td>0</td>
<td>91.4</td>
<td>31.2</td>
</tr>
<tr>
<td><strong>MICROALBUMIN DIPSTICK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microalbumin dipstick at 20m/l</td>
<td>83.3</td>
<td>43.8</td>
<td>35.7</td>
<td>87.5</td>
<td>56.3</td>
<td>16.7</td>
<td>54.6</td>
</tr>
<tr>
<td>Microalbumin dipstick at 50mg/l</td>
<td>85.4</td>
<td>88.9</td>
<td>94.6</td>
<td>72.7</td>
<td>11.1</td>
<td>14.6</td>
<td>86</td>
</tr>
<tr>
<td>Microalbumin dipstick at 100mg/l</td>
<td>30.2</td>
<td>94.7</td>
<td>94.7</td>
<td>30.5</td>
<td>5.5</td>
<td>69.5</td>
<td>46.2</td>
</tr>
<tr>
<td>Microalbumin dipstick at &gt;100mg/l</td>
<td>3.4</td>
<td>100</td>
<td>100</td>
<td>24.4</td>
<td>0</td>
<td>96.7</td>
<td>26.3</td>
</tr>
<tr>
<td><strong>MICROALBUMIN/CREATININE RATIO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>95.1</td>
<td>89.5</td>
<td>96.7</td>
<td>85</td>
<td>10.5</td>
<td>4.9</td>
<td>93.8</td>
</tr>
</tbody>
</table>

**PPV**=POSITIVE PREDICTIVE VALUE  
**NPV**=NEGATIVE PREDICTIVE VALUE  
**FPR**=FALSE POSITIVE RATE  
**FNR**=FALSE NEGATIVE RATE
There were a total of 80 inpatients with 80 urine samples. Collection of urine started at 9am. Table I shows socio-demographic data for patients. Of the 80 subjects recruited for the study, the age groups 25-29 years and 30-34 years contributed the highest percentages 36.3%, followed by the group 20-24 years (15%). Majority of the subjects were nulliparas (51.3%), followed by primiparas (20%). Most of the patients studied were Christians (95%) while Muslims were 5%. Majority of the subjects had tertiary education (47.5%), followed by secondary education (41.3%). The occupation of the patients' husband were mostly trading (50%), followed by civil service (17.5%). Most of the fetuses were between 34-36+6 weeks.

All the patients that had between 3+ and 4+ proteinuria from urine dipstick, had significant proteinuria in 24 hour urine protein (table IIa). The sensitivity of urine dipstick was 72.1%, specificity, 68.4%. The positive predictive value was 88% while the negative predictive value was 43.3%. The false positive rate and the false negative rate were 31.6% and 27.8% respectively. The accuracy was 71.3% (Table IIb).

All the patients that had microalbumin level >100mg/l had significant proteinuria in 24hour urine sample. The test of validity and reliability for positive microalbuminuria were sensitivity (98.3%), specificity (36.8%), positive predictive value (83.3%), negative predictive value (87.5%), false
positive rate (63.1%), false negative rate (1.6%), and accuracy (83.7%).(Table IIIb)

The sensitivity and specificity for the urinary microalbumin/creatinine ratio were 95.1% and 89.5% respectively (Table IV). The positive predictive value was (96.7%), the negative predictive value was (85%). The false positive rate and the false negative rate were (10.5%) and (4.9%) respectively. The accuracy was (93.8%).

The sensitivity of the various tests showed that the microalbumin dipstick had the highest value of 98.4%, closely followed by microalbuminuria/creatinine ratio (95.1%). Urine dipstick has the lowest sensitivity (72.1%). (table vii). Microalbuminuria/creatinine ratio has the highest specificity of (89.5%), while the microalbumin dipstick was the least (36.8%). The false positive rate was highest with microalbumin dipstick (63.2%) and lowest with microalbuminuria/creatinine ratio (10.5%). The false negative rate was highest with urine dipstick (27.9%) and lowest with microalbumin dipstick (1.6%). The positive predictive value for microalbuminuria/creatinine was very high (96.7%), while the visual dipstick was (88%) and microalbumin dipstick was (83.3%). The negative predictive value was highest with microalbumin dipstick (87.5%), was (85%) for microalbuminuria/creatinine ratio and least with visual dipstick (43.3%). The accuracy of
microalbuminuria/creatinine ratio was remarkable(93.7%), and lowest with visual dipstick(71.3%). (Table V)

Table VI is a comprehensive table that summarized the validity and reliability of various tests at different positive levels compared to 24 hour urine protein. The visual dipstick at 3+ and 4+ have specificity of 100% but very low sensitivity(8.6%) and (4.9%) respectively. Their false positive rate were remarkably low(0%). The positive predictive value at 4+ was 100%, however the accuracy was (27.5%). Similar findings were noted with microalbumin dipstick at level >100mg/l. The microalbuminuria/creatinine ratio has very high sensitivity (95.1%), specificity (89.5%), positive predictive value (96.7%), Negative predictive value(85%) and accuracy(93.8%), moreso, it has very low false negative rate(4.92%) and false positive rate(10.5%).

In terms of cost, the cheapest test was the visual dipstick test ($0.5), followed by microalbumin dipstick($2). Both were very easy and quick to carry out (immediately). The microalbuminuria/creatinine ratio was more expensive($5) which took about 30mins to carry out. The 24 hour protein estimation cost $3 and the result is available about 25 hours.
Discussion

The socio-demographic variables shows that the peak age range was 25-34 years (72.5%), primigravidae contributed the commonest parity (51.25%) and the peak gestational age was at 34-36+6weeks (75%). Most patients were Christians (95%) and peak education level was tertiary (47.5%). Primigravidae have been demonstrated by numerous workers to be at high risk of developing pre-eclampsia\textsuperscript{1,22}. The peak age of 25-34 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 preterm hence the 75\% that had their deliveries at preterm is not surprising, though delivery from 34 weeks is managed as term. Most patients were Christians because Christianity is the predominant religion in the environment where the study was carried out.

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. 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. The proteins excreted in urine of preeclamptic women are, however, heterogeneous and variable such as albumin, immunoglobulins, Tamm-Horsfall glycoprotein and in some cases do not even include albumin. 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 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 microalbuminuria/Creatinine ratio, urinary microalbumin dipstick and the urinary visual dipstick test with the standard 24-hour 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 microalbuminuria/creatinine ratio with a sensitivity of 95.1% 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 microalbumin dipstick was much higher 98.3% which means that it can identify almost all significant proteinuria.

The sensitivity of urine dipstick is lowest at 72.1%. 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 very low for the microalbuminuria/ creatinine ratio at 4.9% and even lower with urin microalbumin dipstick 1.6%. Missed diagnosis of preeclampsia is highest 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 white 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 more than 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 27.9% for dipstick test found in this study is similar to a rate of 28% 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 microalbumin dipstick had the lowest specificity of 36.8%, followed by visual dipstick 68.4%. The microalbuminuria/creatinine ratio has a specificity of 89.5% a false positive rate of 10.5%. Dipstick tests had a false positive rate of 31.6% which is about three times that of the spot urinary microalbuminuria/creatinine ratio (10.5%). While urine microalbumin dipstick has false positive rate of 63.2% which is over six times that of urinary microalbuminuria/creatinine ratio. This implies that greater than 50% of patients without proteinuria are incorrectly identified in a clinical setting if both dipstick test are 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 dipsticks are unreliable for clinical decision making. While the false positive rate for the urinary protein/creatinine ratio of 10.5% 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 dipsticks 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 microalbuminuria/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 microalbuminuria/creatinine ratio
(96.7%), is higher than that for the dipstick test (88%). 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
microalbuminuria/creatinine ratio is low.
The negative predictive value of dipstick is lower than its positive predictive value (43.3% versus 88%). This has significant implications for clinical practice. Hence the probability that a negative dipstick reaction is genuinely negative is much lower than the probability that a positive result is positive—a negative result is less reliable than a positive one. However, the negative predictive value of urine microalbumin dipstick test was found to be similar (87.5%) to the microalbuminuria/creatinine ratio (85%), hence, a negative result with these rapid diagnostic tests have 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 highest for the microalbuminuria/creatinine ratio (93.8%) compared to the urine microalbumin dipstick test (83.8%), and visual dipstick test (71.3%).

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 microalbuminuria/creatinine ratio is almost 5
times the cost of urinary dipstick. The result of the dipsticks results are gotten immediately, while the microalbuminuria/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 microalbuminuria/creatinine ratio, require laboratories and trained laboratory personnel. The microalbuminuria/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.
CONCLUSION

The result of this study demonstrate that in hospital with appropriate laboratory personnel and where patients can afford it, routine use of either the microalbuminuria/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 microalbuminuria/creatinine ratio which has better correlation with the 24 hour urine protein.

The microalbuminuria/creatinine ratio especially is reliable, relatively faster and accurate for proteinuria correlating well with 24-hour 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.

From this study, urine microalbumin dipsticks alone was found to have better reliability and validity profiles compared to visual dipstick, and affords quick, easy and immediate result with slight marginal increase in cost. It should replace visual dipsticks or can be used in combination to synergise each other, when microalbuminuria/creatinine ratio cannot be offered readily.
RECOMMENDATION

This study has shown that microalbuminuria / creatinine ratio is over and above better than visual dipsticks in reliability and validity in detecting significant proteinuria in preeclampsia and correlates very well with 24-hour urine protein. However, this facility is not available for ready use. There is need to provide these materials in hospitals to aid diagnosis.

There is need to train laboratory personnel and for government to subsidize the cost of this investigation to encourage its wide use and to aid immediate and prompt intervention thereby preventing underdiagnosis or overdiagnosis with its attendant outcome. Microalbuminuria / creatinine ratio are now available as automated dipsticks and since this study has validated its clinical efficacy in detecting significant proteinuria, it is my recommendation that it should replace visual dipsticks and protocol for its use made available in all health institutions.

Further studies needed to be carried out using microalbuminuria / creatinine ratio in other centres in Nigeria in order to correlate their results with this study.
REFERENCES


APPENDIX I

CONSENT FORM FOR THE PATIENT

TITLE OF RESEARCH: ACCURACY OF SPOT URINARY MICROALBUMINURIA: CREATININE RATIO COMPARED TO 24 HOUR URINE PROTEIN IN DETECTING PROTEINURIA IN PRE-ECLAMPSIA

Hospital Number:

Name of Patient:

1. I confirm that I have been adequately counselled and understand the purpose for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.

3. I understand that sections of my medical notes and those of my baby/babies may be looked at by responsible individuals involved in the study. I give permission for these individuals to have access to these records.

4. I agree to take part in the above study.

Name of patient Date Signature/thumbprint

Name of investigator Date Signature.
APPENDIX 1

Questionnaire/Data Sheet: Accuracy of the Spot urinary Microalbuminuria:
Creatinine Ratio compared to 24 hour urinary protein in detecting proteinuria in pre-eclampsia.

Thank you for taking part in this study about Spot Microalbuminuria: Creatinine Ratio Validation. The questionnaire is voluntary and anonymous. The information provided will be treated as strictly confidential. Some of the questions are rather personal character. We hope that this will not make it difficult to answer.

Section A: Social Demographics
1. Study number: ________________
2. Hospital: ________________
3. Age: ________________
4. Parity: ________________
5. Religion: ________________
6. Occupation: ________________
7. Level of Education: ________________
8. Husband’s Occupation: ________________
9. Gestational Age at Entry: ________________
10. Height: ________________
11. Weight: ________________
12. Blood Pressure:------------------------mmHg

Section B: Risk Factors
13. Are you in a new marriage? Yes/No
14. Have you had previous history of raised Blood Pressure or Protein in Urine during Pregnancy or birth? Yes/No
15. If Yes at what gestational age? ___________________

16. Has anybody in your family ever convulsed during pregnancy or after delivery? Yes/No

17. Any family history of hypertension? Yes/No

18. How many fetuses are you carrying in this index pregnancy?

19. What is your blood group? ___________________

20. Have you had history of recurrent pregnancy losses in the past? Yes/No

21. Are you on any medications? Yes/No
   If Yes specify __________________

22. Do you smoke? Yes/No
   If Yes, what quantity in a day? ______________

23. Do you have history of neck swelling? Yes/No

24. Do you feel cold or hot when people around you are feeling otherwise? Yes/No

Section C: (For Private use By Investigator)

25. Visual Dipstick

<table>
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<tr>
<th>Nil</th>
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Specific gravity _______ pH ________
26. Microalbumin Dipstick

<table>
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<tbody>
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<td>Neg</td>
<td>&lt;20mg/L</td>
</tr>
<tr>
<td>20mg/L</td>
<td></td>
</tr>
<tr>
<td>20 – 50mg/L</td>
<td></td>
</tr>
<tr>
<td>50mg/L</td>
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</tr>
<tr>
<td>50 – 100mg/L</td>
<td></td>
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<tr>
<td>100mg/L</td>
<td></td>
</tr>
<tr>
<td>&gt;100mg/L</td>
<td></td>
</tr>
</tbody>
</table>

27. Laboratory Qualifications

a. Creatinine:-----------------------------

b. Creatinine Clearance (Calculations):-----------------------------

28. Microalbumin/Creatinine Ratio:-----------------------------

29. 24 Hour Urinary Protein Value:-----------------------------