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RESEARCH DISSERTATION

ON

ASSOCIATION BETWEEN CA125 LEVELS AND PREECLAMPSIA IN SOUTH WEST NIGERIA

SUBMITTED IN PART FULFILLMENT OF THE REQUIREMENTS FOR THE FMCOG PART II EXAMINATION OF THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA

BY

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NOVEMBER, 2014
ASSOCIATION BETWEEN CA125 LEVELS 
AND PREECLAMPSIA IN SOUTH WEST 
NIGERIA

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This dissertation by Dr. Bankole Gbemisola in part fulfillment of the requirements for the FMCOG II of The National Postgraduate Medical College of Nigeria was supervised by me.

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I am grateful to everyone who has contributed in one way or the other in making me what I am today.

Above all, my gratitude goes to God who has made all things possible.
ABBREVIATIONS USED IN THE TEXT

The following are the full meanings of some abbreviations used in this book:

BP  Blood Pressure
CA125  Cancer Antigen 125
cm  Centimetre
cm$^3$  Cubic centimeter
CRP  C-Reactive Protein
dl  Decilitre
EDTA  Ethylene Diamine Tetra-acetic Acid
EGA  Estimated Gestational Age
ENND  Early Neonatal Death
ELISA  Enzyme-linked Immunosorbent Assay
g  Gramme
g/L  Gramme per litre
Hb  Haemoglobin
HCl  Hydrochloric Acid
HDP  Hypertensive Disorders of Pregnancy
HELLP  Haemolysis Elevated Liver enzymes and Low Platelets
HRP  Horseradish Peroxidase
IL  Illinois
IU  International units
IU/mL  International Units per Millilitre
IUDFD  Intra-uterine fetal death
IUGR  Intrauterine Growth Restriction
LUTH  Lagos University Teaching Hospital
mg/dl  Milligramme per decilitre
ml  Millilitre
mm  Millimetre
mmHg  Millimetres of mercury
mmol/l  Millimol per litre
NHBPEP  National High Blood Pressure Education Program
NHLBI  National Heart Lung and Blood Institute
NK                      Natural Killer Cells
n (or N)                Number
No.                     Number
P                       Proportion
pp                      Pages
SCBU                    Special Care Baby Unit
SD                      Standard Deviation
SPSS                    Statistical Package for the Social Sciences
sFlt-1                  Serum fms-like Tyrosine Kinase
TB                      Tuberculosis
USA                     United States of America
%                       Percent
µmol/l                  Micromol per litre
µL                      Microlitre
χ²                      Chi-square
<                       Less than
>                       Greater than
≥                       Greater than or equal to
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ABSTRACT

Background: Hypertensive disorders of pregnancy which include preeclampsia is a major contributor to maternal mortality worldwide. Every year, preeclampsia accounts for 100,000 maternal deaths worldwide and this high incidence makes its prevention and effective management very important. Numerous early predictors and biomarkers for this pregnancy complication have been postulated but none is yet to find universal acceptance.

Objective: This study compared levels of maternal serum CA125 in normal pregnancies and pregnancies complicated with preeclampsia to see if there is any relationship or relevance of this marker with preeclampsia, its diagnosis and/or management.

Design: A Comparative study comprising of 70 pregnant women with preeclampsia (cases) and 70 normotensive women as controls.

Methodology: Using a proforma, information on the socio-demographic data and obstetric profile were obtained from both cases and control. 5 mls of maternal venous blood was collected after obtaining consent from both cases and control. All the women were followed up till delivery and records of the delivery and neonatal outcomes were obtained subsequently. Serum CA125 levels were determined by standard enzyme-linked immunosorbent assay (ELISA). Statistical analysis was done using SPSS version 19 software package.

Results: The mean age of the cases was 31.90±4.49 years while that of the controls was 31.24±4.92 years. Majority of the patients were nulliparous in both groups. The mean concentration of serum CA125 among cases is 53.17±26.18 iu/ml while the mean concentration among controls is 12.49±6.62iu/ml. This was statistically significant with a p value of 0.0001. Using the cut-off point of 50IU/ml for serum CA125 concentrations as suggested by Mustafa et al17 the sensitivity, specificity, positive and negative predictive values of using this biochemical marker were 54.2%, 100%, 100% and 68.6% respectively.

The mean birth weight for cases was 2.13±0.82kg and 3.12±1.01kg amongst the controls (pvalue 0.01). Low birth weight babies were detected in 12(18.57%) of the babies of women with preeclampsia and in none of the controls (p=0.001).There were 6(8.6%) still births and 64(91.4%) live births for the women with preeclampsia (p= 0.01). 29 (45.31%) required admission into the special care baby unit (SCBU) where 10(15.63%) of them suffered an early neonatal death (p=0.001). 100% live birth rate was seen among the controls,7 babies required SCBU admission amongst the controls with no ENND in any of the babies.

Conclusion: CA125 is elevated in preeclampsia when compared with normal pregnancy.
INTRODUCTION

Hypertensive diseases in pregnancy is the third commonest cause of maternal mortality worldwide.\textsuperscript{1} It accounts for about 12\% of maternal deaths.\textsuperscript{1,2} Approximately 5\% of pregnancies are affected by preeclampsia, making it one of the most common medical complications of pregnancy.\textsuperscript{3} The World Health Organization estimates that over 100 000 women die from preeclampsia each year globally, with a higher incidence noted in developing countries (2.8\% of live births) as opposed to developed countries (0.4\%).\textsuperscript{2} In a 10-year review (1986–1995) of maternal deaths in Lagos, preeclampsia/eclampsia was the second most common cause of maternal death responsible for 16.4\% of all maternal deaths and had a case fatality rate of 21.0\%.\textsuperscript{5}

It is also a leading cause of neonatal morbidity and mortality resulting in 500,000 infant deaths globally each year.\textsuperscript{6} In the United States, hypertensive disorders of pregnancy in particular preeclampsia is responsible for 15.9\% of maternal deaths and one-third of all premature births.\textsuperscript{6,7} Complications arising from preeclampsia include, eclampsia, HELLP syndrome (Hemolysis, Elevated Liver Enzymes and Low Platelets), Acute kidney injury (AKI), pulmonary edema, placenta abruption, increased stillbirth rates, intrauterine growth restriction (IUGR), intrauterine fetal death (IUFD) and Early neonatal death (ENND).\textsuperscript{8,9}

Considering the morbidity and mortality associated with preeclampsia, considerable work have been done in identifying useful markers of the disease that might be useful in early diagnosis and prognosis. Some biochemical markers have been investigated in the screening of preeclampsia. These markers are identified on the basis of what is presently known of the pathophysiology of preeclampsia. However, results on the reliability of these tests in predicting or diagnosing preeclampsia have largely not been encouraging. This may not be totally surprising as the pathophysiology of preeclampsia itself is still open to a lot of debate.
Preeclampsia is a syndrome of unknown etiology. It is multifactorial, multiorganic, irreversible in nature and is associated with increased morbidity and mortality to both mother and baby. Definitive treatment of the syndrome is by delivery of the fetus and its placenta. There is a need for early identification of women with preeclampsia as it is a high-risk pregnancy, by so doing, modification of antenatal care and preventive treatment regimens can be put in place to reduce the number of complications and deaths from this disease.

In order to be able to screen for a disease entity, it should have a well understood biology which is however not the case of preeclampsia as its exact pathophysiology is yet to be clearly defined.\textsuperscript{7,14,17}

There is the theory of impaired trophoblastic invasion in the first trimester of patients with preeclampsia, based on this theory, De Groot et al\textsuperscript{21} described that abnormal trophoblastic invasion of the maternal decidua affects the maternal vascular deportation of decidual stromal proteins such as Ca125 and insulin like growth factor binding protein1 (both are major endometrial proteins whose primary sources are decidual epithelial and stromal cells) and detected alterations in their levels.

CA125 (cancer antigen-125) is a cell-surface mucin like coelomic antigen, Its most significant role in present day Obstetrics and Gynaecology is in the early diagnosis and monitoring of epithelial ovarian cancer\textsuperscript{10}. However CA125 levels are not specific for ovarian malignancy as levels above 35 IU/ml have been found in benign gynecological conditions as well as healthy pregnant and non pregnant women. As such, is now being widely investigated as an effective marker for conditions other than ovarian malignancy.\textsuperscript{11,12,13}

This antigen is secreted from normal tissues, such as; coelomic epithelium, amnion and their derivatives: respiratory system, mesenteric organs and epithelium of female genital system.\textsuperscript{14}
An increased CA125 level may be of genital or non-genital origin. Non genital causes include hepatic diseases, peritonitis, tuberculosis, renal failure, breast, colon and lung cancer. Genital causes include; pelvic inflammatory diseases, endometriosis, adenomyosis, leiomyoma, endometrial and ovarian cancer.\textsuperscript{15}

Presently the function of CA125 in pregnancy is poorly understood, and its clinical significance in patients is still controversial.\textsuperscript{10} In pregnancy, the fetal chorion, amniotic fluid and maternal decidua are potential sources of high serum CA125 during the first gestational trimester and puerperal period with levels of CA125 rising during the first trimester and returning to a non pregnancy range during the second and third trimesters.\textsuperscript{15,16,17} Pregnant women frequently exhibit slightly increasing CA125 levels within the first trimester.\textsuperscript{12,18} This appears to be derived from both amniotic fluid and decidua.\textsuperscript{18,19} Intact basal decidua is a determinant of CA125 concentrations in the amniotic fluid such that damage to the decidua, epithelial basement or amniotic membrane may cause an increase uptake of amniotic fluid into maternal circulation therefore causing a rise in maternal CA125 serum concentrations.\textsuperscript{10}

Elevated CA125 levels have also been detected in patients with nonviable pregnancies complicated with vaginal bleeding indicating that a disintegration of the decidua, epithelial basement membrane or amniotic membrane may be suggestive of its potential role as a diagnostic and prognostic marker in symptomatic early gestation.\textsuperscript{10} Ectopic pregnancies have also been found to be associated with extremely low levels of CA125 compared to both viable and non viable pregnancies.\textsuperscript{20} These evidences support the secretion of CA125 at the choriodecidual unit of pregnancy.

The pathophysiological abnormalities associated with preeclampsia include placental dysfunction, widespread endothelial damage and systemic inflammation.\textsuperscript{21} Considering the secretion of CA125 at the choriodecidual unit and derivatives of coelomic epithelium, it is
plausible that assaying values of CA125 may have a role in the early diagnosis of preeclampsia, However, clinical studies related to the use of CA125 in hypertensive disorders of pregnancy are few and report contradictory results.\textsuperscript{10}

A study by Mustafa et al\textsuperscript{17} assumed that the extension of decidual destruction and failure of trophoblastic invasion in preeclampsia may induce the secretion of CA125 within placenta and a corresponding rise in level as seen in preeclamptic women. They concluded that when the cut-off point for serum CA125 concentrations was accepted as 50 IU/ml, the sensitivity and specificity of this biochemical marker were, respectively, 93.7 and 88.0\% for the detection of preeclamptic pregnancies.\textsuperscript{17}

In another study by Cebesoy et al\textsuperscript{22}, the serum concentrations of (C reactive protein) CRP and CA125 were found to be significantly higher in women with preeclampsia/eclampsia when compared with healthy pregnant women. Also serum CRP and CA125 levels of women with severe preeclampsia/eclampsia were significantly higher than those of the women with mild preeclampsia. Significant correlations were also found between CRP, albumin, CA125 and mean arterial pressure leading to their conclusion that CRP and CA125 were elevated in preeclampsia.\textsuperscript{22}

As earlier mentioned, the definitive treatment of preeclampsia is by delivery of the fetus and its placenta especially in the presence of deteriorating maternal condition. Delivery at early gestations, however, is associated with high perinatal mortality and morbidity resulting from prematurity\textsuperscript{1–3} whereas, prolonging pregnancy by expectant management may result in increased maternal morbidity and even mortality\textsuperscript{5,6}. Ultimately the potential benefits for the fetus must be balanced against the potential dangers to the mother, such as death or cerebral haemorrhage. Thus aggressive management policies aimed at improving perinatal outcomes and reducing the incidence of serious maternal complications need to be developed.
At present, the search for tests aimed at predicting future development of preeclampsia in low or high-risk women and the identification of those women whose condition will progress to severe disease or result in adverse pregnancy outcome is needed in modern day obstetric practice.\textsuperscript{23}

There is paucity of data as regards to CA125 and its relationship with preeclampsia. The Aim of this present study is to therefore determine the level of CA125 antigen in normal and preeclamptic pregnancies and thus determine if there is any relationship between it and preeclamptic pregnancies and its potential of being used as a marker for the disease.
LITERATURE REVIEW

Hypertensive disorders of pregnancy (HDP) account for more than 50,000 maternal deaths per year worldwide. With an incidence of 12% to 18%, HDP are the second commonest cause of antenatal and postnatal deaths in industrialized countries. They are also implicated in 20% to 25% of perinatal mortality.\(^1,24\) Of greatest importance is preeclampsia/eclampsia, characterized by hypertension, proteinuria and/or organ dysfunction, which complicates between 2% and 5% of all pregnancies, 10% of first pregnancies, about 7% in women who have previously had children, and in 20-25% of women with a history of chronic hypertension.\(^1,3,25\). It is a cause of high morbidity for both mother and fetus, especially in developing countries.\(^26\) The prevalence of preeclampsia in developing countries ranges from 1.8% to 16.7%. Severe cases of preeclampsia and eclampsia are very common in Nigeria with a prevalence ranging between 2% to 16.7%.\(^27-29\) An incidence rate of 3-9% in the north and approximately 1-3% in the south.\(^30\) In northern Nigeria preeclampsia/eclampsia accounts for up to 40 percent of maternal deaths. In a study conducted at the Lagos University Teaching Hospital in 2005, preeclampsia accounted for 7.6% of total number of deliveries.\(^31\)

Hypertensive disorders complicating pregnancy is classified into the following 4 categories according to the National High Blood Pressure Education Program (NHBPEP 2001) of the National Heart Lung and Blood Institute (NHLBI 2001):

1. Gestational hypertension—(previously pregnancy induced hypertension.) This is elevated BP (in the absence of proteinuria) first detected after the twentieth week of pregnancy.
2. Preeclampsia and eclampsia syndrome
3. Preeclampsia syndrome superimposed on chronic hypertension
4. Chronic hypertension.
It can be difficult to diagnose this syndrome when women initially seek prenatal care late in pregnancy. Women diagnosed with gestational hypertension may eventually fulfill diagnostic criteria for preeclampsia if proteinuria subsequently develops. In the absence of proteinuria, chronic hypertension is diagnosed when the BP remains elevated six weeks postpartum, while transient hypertension of pregnancy is diagnosed when the BP normalizes postpartum.\textsuperscript{32}

About 22\% of chronic hypertensives may develop superimposed preeclampsia with impaired prognosis while up to 50\% of gestational hypertensives can progress to preeclampsia.\textsuperscript{33,34,35} Close monitoring in the antenatal period is necessary for these 2 groups of patients.

The criteria for diagnosis of HDP is as follows: a systolic blood pressure of ≥140mm Hg and/or a diastolic blood pressure of ≥90mm Hg, in two readings taken over a period of 4 to 6 hours after 20 weeks gestation, in a woman who was normotensive prior to pregnancy.\textsuperscript{36,37} The use of the sphygmomanometer remains the gold standard for measuring blood pressure.\textsuperscript{36,38}

The Korotkov phase V (disappearance of the blood flow murmur) is the reliable means of measuring diastolic blood pressure in pregnancy. If the diastolic pressure according to this means is zero (up to 15\%), then the Korotkov sound IV (the quietening/muffling of the blood flow murmur) should be used.\textsuperscript{36,38,39}

Proteinuria is defined as two midstream urine specimens taken more than 4 hours apart with 2+ protein on dipstix testing or 1+ protein with measured specific gravity of >1.03 and pH <8. However, In view of the high false positive rates with dipsticks, laboratory testing usually by 24-hour urine collection is recommended to confirm significant proteinuria.\textsuperscript{38}
Severe preeclampsia is defined as severe hypertension confirmed with a diastolic blood pressure $\geq 110$ mmHg on two occasions or systolic blood pressure $\geq 170$ mmHg on two occasions together with significant proteinuria (at least 1 g/litre) or $\geq 5$g/24 hours$^{38,40}$.

Clinical features of severe preeclampsia will include:

- Deterioration of renal function: serum creatinine greater than 0.9g/L or oliguria <500mL/day
- Liver involvement: severe epigastric pain and/or elevated transaminases
- Pulmonary edema
- Hematological involvement: thrombocytopenia, hemolysis, disseminated intravascular coagulation, platelet levels below $100\times10^6$ (HELLP Syndrome)
- Neurological involvement: severe headache, persistent visual disturbance, hyperreflexia.
- Intrauterine growth restriction.

PATHOPHYSIOLOGY

The exact pathophysiologic mechanism of pre eclampsia is not clearly understood. In most cases, pathology demonstrates evidence of placental insufficiency with associated abnormalities such as an inflammatory placental decidual vasculopathy, diffuse placental thrombosis, and/or abnormal trophoblastic invasion of the endometrium$^{41,42}$. There is an increase in production of reactive oxygen species, increased release of inflammatory cytokines, abnormal activation of clotting system and activated circulating leukocytes.$^{43}$

Described in a two stage process, the pathogenesis of preeclampsia involves: the preclinical (the first 20 weeks’ gestation) and the clinical (normally after 20 weeks’ gestation)$^8$. The first stage or preclinical occurs soon after implantation when there is inadequate invasion by a subtype of trophoblasts described as extravillous cytotrophoblasts.$^8,43$ The second or clinical
stage of preeclampsia is heralded by the effects of a generalised inflammatory response originating from an oxidatively stressed or hypoxic placenta resulting from incomplete remodeling of the maternal spiral arteries into low resistance dilated vessels. This oxidative stress within the placenta causes the release of such factors as sFlt-1 (serum fms-like tyrosine kinase), soluble endoglin, pro-inflammatory cytokines, and even trophoblast debris: all of which lead to a systemic inflammatory response in the mother. This inflammatory milieu causes generalised endothelial dysfunction which manifests in various key organs of the mother causing the classic syndrome of preeclampsia.8,42,43,44

CA125 And Preeclampsia

CA125 is an antigenic determinant recognized by the murine monoclonal antibody OC125 quantified by radioimmunoassay.22,45 It is a sensitive but non specific tumor marker useful in the management of ovarian malignancies11,12,46. The role of CA125 in pregnancy is yet to be clarified but its serum values were significantly higher in the first and the third trimesters of pregnancy when compared to those in the second trimester.12,24

There are two theories explaining the rise of maternal serum CA125 in the first trimester. The most accepted theory about the rise of CA125 antigen in the blood during pregnancy is the tubal reflux theory of Quirk et al.48 This theory says CA125 is of decidual origin and passes to maternal compartment via tubal reflux. It rises in the circulation after absorption by peritoneal lymphatics as the pregnancy proceeds, a functional obstruction then occurs due to the fusion of deciduas capsularis and deciduas parietalis in tuba uterine, and serum CA125 levels begin to decrease.47,48 The second theory is explained as the passage of CA125 to the maternal blood circulation due to the damage in decidual cells made by the chorionic villus invasion in early pregnancy and by the separation of placenta at birth10. The cause of the
increase of CA125 in the maternal circulation at in-utero death is related to damage in the decidua.\textsuperscript{10} This also explains the rise in CA125 levels in threatened miscarriages.

CA125 is also elevated in the serum of patients with diseases associated with peritoneal or pleural effusion and subsequent formation of ascites.\textsuperscript{11,22,45} The presence of both ascites and high levels of serum CA125 is suggestive of a possible hepatic disease or disease affecting hepatic functions.\textsuperscript{21,22,45} The presence of ascites was thought to be the major cause of the elevation in CA125 levels in ovarian malignancies and hepatic diseases.\textsuperscript{45}

In preeclampsia, decreased level of albumin (due to proteinuria and hepatic dysfunction) is thought to be related with edema and ascites in these patients. According to Cebesoy et al\textsuperscript{22} a theory of the hypoalbuminemia (protein loss and production insufficiency) in preeclamptic women resulting in ascites and a possible increase in CA125 levels is entertained.

Serum concentrations of CA125 are increased early in pregnancy and immediately after birth, this is said to be due to the disintegration of the maternal decidua. Therefore, an extension of decidual destruction and separation of trophoblasts from deciduas are proposed as the underlying mechanism for the elevation in CA125 in preeclamptic women.\textsuperscript{49,50}

In pregnancies that were complicated with preeclampsia, it is assumed that the failure in trophoblastic invasion and the induction of an inflammatory process within placenta may trigger the expression of CA125 suggesting that CA125 is a possible biochemical marker which reflects the severity of the underlying inflammatory process in preeclampsia.\textsuperscript{17}

In a recent study carried out by Tyler et al in July 2012\textsuperscript{51} an increased binding of CA125 was found on immune cells of pregnant women and women with preeclampsia. It was concluded in this study that the increased binding of CA125 to these immune cells mainly the NK cells
and monocytes made maternal tolerance of the fetus possible in preeclampsia thus highlighting a possible role for CA125 as a biomarker for the disease.⁵¹
AIM AND OBJECTIVES

Primary Objective:

1. To determine if there is any relationship between CA125 and preeclampsia.

Secondary Objectives

1. To determine the level of CA125 in normotensive pregnant women.
2. To determine the level of CA125 in preeclamptic pregnant women.
3. To compare the levels of CA125 in preclamptic and normotensive pregnant women.

SOURCE OF FUNDING

Self-sponsored.
METHODOLOGY

STUDY AREA
This study was conducted at the maternity unit of the Lagos University Teaching Hospital (LUTH), Idi Araba, Lagos, Nigeria. LUTH is a tertiary institution and referral centre located in the Lagos mainland acting majorly as a referral centre for hospitals in both the public and private sectors of Lagos state.

STUDY POPULATION
Cases included all women diagnosed with preeclampsia in their pregnancy. The control group included women of comparable gestational age and parity to the cases with normal singleton pregnancies.

Preeclampsia was diagnosed in patients with Hypertension earlier described as an absolute blood pressure greater than 140/90 mmHg after 20 weeks gestation (measured using a mercury sphygmomanometer) on at least two occasions 4 hours apart and Proteinuria defined as greater than 0.3 g of urinary protein excretion per 24hour urine collection or ≥ 1 + on dipstick on at least two occasions (≥ 4 h apart) without urinary tract infection. Preeclampsia was classified as severe if systolic blood pressure increased to at least 160mmHg, diastolic blood pressure increased to at least 110mmHg, and proteinuria was >5g/day. Controls were obtained by selective sampling of women with normal uncomplicated pregnancies who do not have preeclampsia.

STUDY DESIGN
This research was a comparative study.
SAMPLE SIZE DETERMINATION

The sample size ‘N’ was calculated using the WINPEPI software for comparing two independent samples.\(^1\) Using the software WINPEPI and selecting Compare2, then sample size and then S1, the following parameters were selected:

- Significance level = 5 per cent (\(\alpha=0.05\))
- Power = 90 per cent (\(\beta=0.1\)).
- Proportion 1 (P1) = 12% (0.12);
- Proportion 2 (P2) = 37% (0.37).
- Allowance was made for an attrition rate of 10 percent

\(P_1=\) Prevalence of elevated CA125 among controls – 0.12 (The value of \(P_1\) was obtained from the study conducted by Mustafa et al where the control group had a 12% prevalence of elevated CA125 above the cut-off of 50iu/ml.\(^1\)

\(P_2=\) Estimated prevalence of elevated CA125 among cases – 0.37 (\(P_2 = 0.37\) Assuming a difference of 25% (0.25) between normal pregnancy and those with preeclampsia)

The minimum sample size calculated was 61 per group, which was expanded by 10% to 67 per group to allow for attrition, and rounded up to 70 per group. Hence, the sample size (N) for this study was 70 participants per group, giving a total of 140 participants.

SAMPLING TECHNIQUE

All patients who presented with preeclampsia who met the eligibility criteria were recruited as cases for the study until the sample size was reached. Controls were women with uncomplicated pregnancies managed at the Lagos University Teaching Hospital.

ELIGIBILITY CRITERIA

This was designed to increase uniformity among the study population and exclude bias.
INCLUSION CRITERIA

For the cases:
- Pregnant women attended to in antenatal clinic, labour ward and emergency unit and diagnosed with preeclampsia.
- The index pregnancy was a singleton without any prior knowledge of congenital anomaly or chromosomal abnormality.
- Pregnant women who have gave an informed verbal and or written consent.

For the control group:
- The patients were normotensive patients of comparable parity and gestational age to the study group.
- The patient had no known medical problem in pregnancy.
- The index pregnancy is singleton without any known congenital anomaly or chromosomal abnormality.
- Informed verbal and/or written consent has been given.

EXCLUSION CRITERIA

- Pregnant woman with diabetes mellitus, chronic hypertension, peripheral vascular disease and/or antihypertensive treatment.
- Pregnant women with multiple gestation.
- Pregnant women with coexisting TB in pregnancy, ovarian cyst and fibroids in pregnancy.
DATA MANAGEMENT

DATA COLLECTION

An informed consent was obtained from all participants after explanation of the purpose and methodology of the research. Patients too ill to be interviewed at first contact were interviewed upon recovery. Using a structured proforma, relevant data was obtained such as the socio-demographic characteristics, parity and estimated gestational age (EGA) calculated based on the last menstrual periods of the participants or from early ultrasound scan done. The medical history, previous obstetric history and treatment regimens received were noted. Pregnancy outcome was obtained by extracting information about the antenatal, labor, delivery and newborn notes from the delivery records. Fetal outcomes such as the birth weight, intrauterine demise and special care baby unit admissions were noted.

Systolic and diastolic blood pressures measurements were taken with a standard mercury sphygmanometer and measured to the nearest 10mmHg of mercury. The protein in urine was tested for using acid test strip (combi 10) by Roche.

The CA125 sample was obtained by collecting 5ml of venous blood from the participants under aseptic condition via venepuncture using a 5ml sterile disposable syringe and needle into a Lithium heparin bottle and transported from the point of collection (Labour ward, emergency room and/or lying in ward) to the central research laboratory of the hospital where it was centrifuged for 10 minutes at 2000rpm using a refrigerated centrifuge. The resulting supernatant (i.e plasma) was transferred into clean polypropylene tubes using a Pasteur pipette in 0.5mls aliquots and stored in the freezer at a temperature of -20°C until the sample size was achieved following which analysis was carried out.
The CA125 levels in were then assayed enzymatically with the ELISA (enzyme linked immunosorbtent assay) method using reagents obtained from the manufacturer (PANOMICS INC. 94555 Carlifornia USA).

**SAMPLE ANALYSIS**

**Principle**

The CA125 ELISA test is based on the principle of a solid phase enzyme-linked immunosorbent assay which utilizes a monoclonal antibody directed against a distinct antigenic determinant on the intact CA125 molecule. A rabbit anti-CA125 antibody conjugated to horseradish peroxidase (HRP) is in the antibody-enzyme conjugate solution. The test sample is allowed to react simultaneously with the two antibodies, resulting in the CA125 molecules being sandwiched between the solid phase and enzyme-linked antibodies. After incubation at 37 °C for 90 minutes, the wells are washed with water to remove unbound labelled antibodies. A solution of TMB Reagent is added and incubated for 20 minutes, resulting in the development of a blue colour. This colour development is stopped with the addition of Stop Solution changing the color to yellow. The concentration of CA125 is directly proportional to the colour intensity of the test sample. Absorbance is measured spectrophotometrically at 450 nm.

**Reagents Composition and Storage.**

Reagent comprises of : Murine Monoclonal anti-CA125 coated microtiter plate with 96 wells.

- Enzyme Conjugate Reagent, 13 ml
- CA125 reference standards containing; 0, 15, 50, 100, 200, and 400 Unit/ml of CA125, 1 ml each, ready to use.
- TMB Reagent (One-Step), 11 ml
- Stop Solution (1N HCl), 11 ml
The ELISA test kit was stored at a temperature of 2-8°C and the microtitre test plates in an air tight bag with desiccants to minimize exposure to damp air. Reagent kits stored as directed by the manufacturer remain stable until the posted expiration date on the label.

**Procedure**

100 µL of CA125 standards, specimen and controls were dispensed into the appropriate wells (there are 96 wells in a microtiter plate) followed by 100µL of the enzyme conjugate reagent into each well. These were allowed to mix gently for 30 seconds and then to incubate. was discarded by emptying the plate contents into a waste container and the microtiter plate was rinsed and emptied 5 times with distilled deionized water (wash buffer) this was done to remove unbound labelled antibodies. The microtiter plate was struck on to absorbent paper or paper towels to remove all residual water droplets.

100µL of the TMB reagent is now dispensed unto each well, mixed gently and allowed to stand in the dark at room temperature for 20 minutes and this reaction was then halted by adding 100µL of Stop Solution into each well, it was again mixed gently for 30 seconds ensuring that all the blue colour changed to yellow completely. The optical density was then read with a microtiter plate reader within 15 minutes.

The mean absorbance values for each set of reference standard, controls and samples were calculated. Following which the absorbance values of the reference standard was plotted against its concentration in U/ml to obtain a standard curve (absorbance on the vertical axis ‘y’ and concentration on the horizontal axis ‘x’) and from this, the corresponding concentration of CA125 in U/ml was extrapolated using the mean absorbance value for each sample.

Normal healthy women are expected to have CA125 assay values below 35 U/ml. The minimum detectable concentration of CA125 in this assay kit is estimated to be 2 U/ml. For
the purpose of this study values above 50U/mL will be used as the detection limit for preeclampsia as suggested in the study by Mustafa et al.\textsuperscript{17}

**STATISTICAL ANALYSIS.**

The collected data was analyzed using Statistical Package for Social Sciences (SPSS 19.0, SPSS Inc., Chicago, IL, USA) in computerized media. Analyses included the use of descriptive statistics such as means, proportions and standard deviation to summarize the quantitative variables. Parametric variables of two groups were compared by independent samples \( t \) test. Data was presented in tables and other appropriate graphical format. Hypothesis testing was done using chi square for categorical variables, and the independent samples \( t \) test for continuous variables with a normal distribution. The level of significance employed for this study is a \( p \)-value of <0.05.

**ETHICAL CONSIDERATION**

The study was carried out after obtaining approval from the Health Research and Ethics Committee of the Lagos University Teaching Hospital. Samples were collected from subjects who gave their written consent for inclusion in the study.

**Informed consent to participate and withdrawal from study**

The purpose of the study was explained to all the potential participants. The willing participants signed an informed consent form. Patients were informed of their freedom to withdraw or refuse to take part in the study without prejudice to their usual expected standard of care.
Confidentiality of data

All information including history, physical findings and results obtained from the participants was kept strictly confidential. The participants were assured that their identity will be kept in confidence by the investigator.

Beneficence of the Study

The samples were collected and sent for analysis at no cost to the participants. The results obtained from this study will help in formulation of evidenced-based policy for prevention and management of preeclampsia.

Non-Malficence

This study did not include any form of interventional measures that may be harmful to the women, either now or in the future. Participant’s blood sample collection from a peripheral vein was the only interventional measure employed and although not harmful, was associated with some discomfort which was duly explained to the participants before collection.

Justice

The participants received equal attention and optimal care throughout this study. Method of participants’ selection was scientifically objective to ensure fairness.

Dissemination of Findings

The results of this study will be submitted as part fulfillment of the requirements for the Part II Fellowship examination of the Faculty of Obstetrics & Gynaecology of the National postgraduate medical College of Nigeria. The study will also be sent for publication after award of the fellowship.

References used are duly recognized in the journal articles, books and electronic materials used for the work. Also thoughts and conclusions of authors were also referenced.
RESULTS

One hundred and forty (140) pregnant women were enrolled in this study, 70 (50%) of them had preeclampsia (cases) while the remaining 70 (50%) had normal pregnancy uncomplicated by hypertension (controls). The mean age of the cases was 31.90±4.49 years while that of the controls was 31.24±4.92 years. See Table 1 below.
Table 1: Sociodemographic Data of Women Enrolled in this Study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cases N=70</th>
<th>Controls N=70</th>
<th>t statistic</th>
<th>Chi square ($\chi^2$)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age (years)</td>
<td>Frequency (%)</td>
<td>Frequency (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>-</td>
<td>1(1.42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-24</td>
<td>2(2.86)</td>
<td>1(1.42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-29</td>
<td>24(34.29)</td>
<td>19(27.14)</td>
<td>11.38</td>
<td>0.128</td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td>26(37.14)</td>
<td>34(48.57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-39</td>
<td>12(17.14)</td>
<td>8(11.43)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 40</td>
<td>6(8.57)</td>
<td>7(10.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Age ±SD</td>
<td>31.9 ± 4.49</td>
<td>31.24 ± 4.92</td>
<td>17.14</td>
<td>0.410</td>
<td></td>
</tr>
<tr>
<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>70(100)</td>
<td>67(95.7)</td>
<td>15.41</td>
<td>0.320</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>Nil</td>
<td>3(4.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No formal education</td>
<td>5(7.1)</td>
<td>9(12.86)</td>
<td>9.31</td>
<td>0.481</td>
<td></td>
</tr>
<tr>
<td>Primary school</td>
<td>24(34.29)</td>
<td>16(22.86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary School</td>
<td>21(30.00)</td>
<td>12(17.14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>University</td>
<td>20(28.57)</td>
<td>33(47.13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Professional/Skilled</td>
<td>8(11.4%)</td>
<td>30(42.8%)</td>
<td>13.51</td>
<td>0.873</td>
<td></td>
</tr>
<tr>
<td>Unskilled</td>
<td>23(32.9%)</td>
<td>20(28.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>39(55.7%)</td>
<td>20(28.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Booking Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Booked</td>
<td>32(45.7%)</td>
<td>64(91.4%)</td>
<td>33.94</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Unbooked</td>
<td>38(54.3%)</td>
<td>6(8.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p values < 0.05 are significant at the 5% significance level (α=0.05)*
Table 2 shows the obstetric variables such as parity and gestational ages for both cases and controls.

**Table 2: Obstetric Variables of Cases and Controls**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cases</th>
<th>Controls</th>
<th>Chi-square ($\chi^2$)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational Age (weeks)</strong></td>
<td><strong>Frequency (%)</strong></td>
<td><strong>Frequency (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28</td>
<td>5 (7.14)</td>
<td>4 (5.71)</td>
<td>0.31</td>
<td>0.564</td>
</tr>
<tr>
<td>28 to &lt; 32</td>
<td>23 (32.86)</td>
<td>21 (30.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33 to &lt; 37</td>
<td>32 (45.71)</td>
<td>34 (48.57)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38 to &lt; 42</td>
<td>10 (14.29)</td>
<td>11 (15.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19</td>
<td>19</td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>1-2</td>
<td>30</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>19</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In table 3 the clinical characteristics of the participants are displayed. Sixty three (90%) of the cases had blood pressure values above 160/110mmHg and proteinuria of 2+ (0.1g/L) and above, placing them in the severe preeclampsia range.
Table 3: Clinical Characteristics of Study Population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cases Frequency (%)</th>
<th>Controls Frequency (%)</th>
<th>Chi-square ($\chi^2$)**</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure (mm/Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 140/90</td>
<td>-</td>
<td>70 (100%)</td>
<td>182.39$^F$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥140/90 to &lt;160/110</td>
<td>7 (10%)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥160/110</td>
<td>63 (90%)</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria (g/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>70 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+ (0.03)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+ (0.1)</td>
<td>37 (52.86%)</td>
<td>0</td>
<td>18.95</td>
<td>0.001*</td>
</tr>
<tr>
<td>3+ (0.3)</td>
<td>33 (47.14%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet Count (cells/µL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 150,000</td>
<td>7 (10%)</td>
<td>0 (0%)</td>
<td>10.93</td>
<td>0.102</td>
</tr>
<tr>
<td>150–400</td>
<td>63 (90%)</td>
<td>70 (100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Uric Acid (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0–4.0</td>
<td>17 (24.28%)</td>
<td>61 (87.14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1–6.0</td>
<td>33 (47.14%)</td>
<td>9 (12.86%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.1–8.0</td>
<td>16 (22.86%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.1–10.0</td>
<td>3 (4.29%)</td>
<td>0</td>
<td>17.86</td>
<td>0.001*</td>
</tr>
<tr>
<td>&gt;10.00</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine (umol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–100</td>
<td>49 (70%)</td>
<td>66 (94.3%)</td>
<td>12.29</td>
<td>0.048*</td>
</tr>
<tr>
<td>101–150</td>
<td>21 (30%)</td>
<td>4 (5.7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p values <0.05 are statistically significant at 5% significance level.

** $\chi^2$ used for hypothesis testing except for blood pressure, indicated by $^F$ where Fisher’s exact test was used as the assumptions of the $\chi^2$ were not met.
The mean birth weight for cases was 2.13±0.82kg and 3.12±1.01kg. Six (8.6%) still births and 64(91.4%) live births were recorded amongst the women with preeclampsia (p= 0.01). Twenty nine (45.31%) required admission into the special care baby unit (SCBU) and 10(15.63%) of them suffered an early neonatal death (p=0.001). Amongst the normotensive women, there were no recorded adverse pregnancy outcomes. See Table 4.

Table 4: Neonatal outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foetal Outcome</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Live Birth n (%)</td>
<td>64 (91.4%)</td>
<td>70 (100%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Still Birth n (%)</td>
<td>6 (8.6%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Birth weight kg (mean ± SD)</td>
<td>2.13 ± 0.82</td>
<td>3.12± 1.01</td>
<td>0.001*</td>
</tr>
<tr>
<td>Low Birth Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12(18.75%)</td>
<td>0 (0%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>No</td>
<td>52(81.25%)</td>
<td>70(100%)</td>
<td></td>
</tr>
<tr>
<td>SCBU Admission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29(45.31%)</td>
<td>7(10%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>No</td>
<td>35(54.69%)</td>
<td>63(90%)</td>
<td></td>
</tr>
<tr>
<td>Early Neonatal death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9 (14.06%)</td>
<td>0(0%)</td>
<td>0.001*</td>
</tr>
<tr>
<td>No</td>
<td>55(85.94%)</td>
<td>70 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

*p values <0.05 are statistically significant at 5% significance level.
The mean concentration of serum CA125 in women diagnosed with preeclampsia was 53.17±26.18 iu/ml while the mean concentration among controls was 12.49±6.62 iu/ml. This was statistically significant with a p value of 0.0001 as seen in Table 5.

Table 5: Serum CA125 levels in both Cases and Controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>Lowest CA125 Level (IU/ml)</th>
<th>Highest CA125 Level (IU/ml)</th>
<th>Mean Serum CA125 Level (IU/ml)</th>
<th>t statistic</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preeclampsia</td>
<td>11.17</td>
<td>96.85</td>
<td>53.17±26.18</td>
<td>9.635</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Control</td>
<td>2.34</td>
<td>21.07</td>
<td>12.49±6.62</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant at the 5% significance level (α=0.05)
Using the cut-off point of 50IU/ml for serum CA125 concentrations as was suggested by Mustafa et al\textsuperscript{17} the sensitivity, specificity, positive and negative predictive values of this biochemical marker were, respectively, 54.2\%, 100\%, 100\% and 68.6\% for the detection of preeclamptic pregnancies (chi-square 52.16, p=0.001). See table 6.

**Table 6: Predictive Power of CA125 in Preeclampsia**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Preeclampsia</th>
<th>Total</th>
<th>Chi-square ($\chi^2$)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CA125&lt;50IU/ml</strong></td>
<td>70</td>
<td>32</td>
<td>102</td>
<td>52.16</td>
<td>0.001*</td>
</tr>
<tr>
<td><strong>CA125\geq50IU/ml</strong></td>
<td>0</td>
<td>38</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>70</td>
<td>70</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant at the 5\% significance level

Positive Predictive Value = 38/38 = 100

Negative Predictive Value = 70/102 = 68.63

SENSITIVITY = 38/70 = 54.2

SPECIFICITY = 70/70 = 100
Table 7: Linear Correlation between CA125 and Clinical/Laboratory Parameters Amongst Patients with Preeclampsia

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pearson’s Co-efficient of Correlation (r)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>0.356</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>0.343</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Urinary Protein</td>
<td>0.325</td>
<td>0.002*</td>
</tr>
<tr>
<td>Platelet Count (cells/µL)</td>
<td>0.341</td>
<td>0.001*</td>
</tr>
<tr>
<td>Serum Uric Acid (mg/dl)</td>
<td>0.048</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

*Statistically significant at the 5% significance level (α=0.05)

Table 7 shows significant positive correlation between CA125 and the clinical and laboratory parameters above.
Figure 1 shows the distribution of CA125 values within the control group and patients with mild and severe preeclampsia. CA125 is markedly elevated in patients with severe preeclampsia in comparison with mild preeclampsia and the control group.

**Figure 1: The Distribution of Elevated CA125 (≥50IU/ml) between Normotensive and Preeclamptic Pregnant Women**

Figure 1 shows that over half 38 (54.3%) of the preeclamptic subjects had CA125 levels above 50IU/ml while none of the controls had elevated CA125.
Figure 2 above shows the distribution of CA125 between control, mild preeclampsia and severe preeclampsia. Elevation in CA125 levels in patients with severe preeclampsia is noted compared with the control group.
Figures 3, 4 and 5 below show pictorial view of the linear correlation between CA125 and systolic blood pressure, diastolic blood pressure and uric acid levels amongst the patients with preeclampsia.

Figure 3: Scatter plot showing positive linear correlation between CA125 levels and systolic blood pressure.
FIGURE 4 Scatter plot showing linear correlation between CA125 and diastolic Blood pressure.
Figure 5: Scatter plot showing positive linear correlation between CA125 and uric acid levels.
DISCUSSION

Preeclampsia is one of the most challenging diseases of obstetrics, probably because of its unknown aetiology, and its multifactorial, multiorganic and irreversible origin. It is a leading cause of maternal and perinatal morbidity and mortality. Several research works have been done to identify a unique biochemical marker that may be used to predict a woman’s risk of developing preeclampsia before the classic symptoms occur, or that may be used as a prognostic indicator. CA125 is a sensitive but non-specific tumour marker used for diagnosis and monitoring of epithelial ovarian cancer. It has been found to be elevated in patients with various diseases; one of such is preeclampsia and it is being suggested as a promising biomarker for preeclampsia, prompting this present study.

This study was conducted amongst women with singleton pregnancies presenting at the Lagos University Teaching Hospital, Idi–Araba, Lagos, a state in the south-western region of Nigeria. The controls were normotensive women of comparable parity and gestational age with the cases. The mean CA125 levels of these women was 12.49±6.62 IU/ml. This finding corroborates Niloff et al study findings where it was discovered that CA125 levels are elevated in the first trimester and then drops and remains below 35IU/ml throughout the rest of pregnancy including immediately prior to delivery in normal uncomplicated pregnancies. The controls in Cebesoy and Karaman studies also had low CA125 values of 14.64IU/ml and 17.2 IU/ml respectively.

The mean CA125 level in the women with preeclampsia was 53.17±26.14 IU/ml this was significantly higher than that in controls (p=0.001). This is similar to studies done by Cebesoy et al, Mustafa et al and Karaman et al who stated in their respective studies that CA125 is elevated in preeclampsia and in particular, severe preeclampsia. In the study by Mustafa et al, the mean serum concentration of CA125 was 55.70±8.72IU/ml and 59.11±4.28IU/ml for
mild and severe preeclampsia respectively, and 48.25±3.34iu/ml for normal pregnancies. Also, in the study by Cebesoy et al, the mean CA125 for normotensive and preeclamptic pregnancy were 14.64 IU/ml and 46.6 IU/ml respectively. Equally significant CA125 values were also observed in Karaman’s study (17.2±8.1 mIU/ml for normal pregnancy, 18.8 ± 8.4 for mild preeclampsia and 38.8±20.9 in severe preeclampsia).

Many studies on CA125 and preeclampsia that have been conducted have shown conflicting results. Schröcksnadel et al were the first to study this relationship, the plasma levels of tumour markers including CA125 were compared in patients with hypertensive disorders of pregnancy, healthy pregnant and healthy non-pregnant controls. CA125 showed no statistically significant differences in the three groups. Bon et al. reported that though maternal serum levels of CA125 were higher during the first and third trimesters of pregnancy, it showed no relationship with preeclampsia. de Groot et al in their study, observed CA125 levels of pregnant women (both normotensives and those who developed preeclampsia subsequently) over a time interval. They found that CA125 did not differ with respect to their pregnancy outcome or gestational age but proposed a possible trend toward an elevation in CA125 concentrations for pregnancies that are destined to develop preeclampsia and called for more studies in this area. Cebesoy et al investigated 54 preeclamptic/eclamptic females and 56 healthy pregnant females and found significantly higher serum concentrations of CA125 and C reactive protein in patients with preeclampsia/eclampsia. They proposed that the elevation of CA125 in preeclampsia is probably due to ascites found in preeclamptic women arising from hypoalbuminemia, a theory Karaman also agreed with. Mustafa et al on the other hand said that failure of trophoblastic invasion with the induction of an inflammatory process within the placenta leads to the expression of CA125 in preeclampsia.
In this study, the threshold cut off value of 50iu/ml was used for detection of CA125 in preeclamptic pregnancies. This cut off was suggested by Mustafa et al for screening of preeclampsia. The sensitivity of using this particular threshold value was 93.7%, specificity 88.0%, positive predictive value 91.7% and negative predictive value of 90.7%. Using this threshold in our study, we obtained a sensitivity of 54.2%, specificity of 100%, a positive predictive value of 100% and a negative predictive value of 68.63%.

In Mustafa’s study, some of the women with normal pregnancy had high CA125 levels, above the threshold used. This would probably have reduced the specificity and the positive predictive value obtained in their study. In this study on the other hand none of the controls had values above the minimum threshold suggested by Mustafa et al thus giving the high specificity and positive predictive value obtained.

Cebeşoy et al in his own study had used a cut off of 35 iu/ml, but Lelle et al in an earlier study had suggested that in pathological pregnancies CA125 measurements should be above the recommended cut off of 35iu/ml.55

This study also shows that CA125 levels are significantly elevated in the patients who had severe preeclampsia in comparison with mild preeclampsia and the normotensive patients, a finding similar to those of Karaman et al53 and Mustafa et al17. According to Cebeşoy et al, CA125 levels were found to be significantly higher in severe preeclampsia and eclampsia compared with mild preeclampsia indicating that CA125 can be used as a valuable marker in preeclampsia and eclampsia follow-up.22

Kalaman et al observed that females diagnosed with preeclampsia had significantly lower birth weight children than those in the control group, a finding also observed in this present study. Women with preeclampsia recorded a poor perinatal outcome compared with the
normotensive group. Mustafa et al also describes a higher need for special care baby unit admission as well as intrauterine growth restriction in the preeclamptic group.\textsuperscript{17} They also found a positive correlation between CA125 concentrations and systolic blood pressure, diastolic blood pressure, platelet count, serum uric acid level and urine protein. This was similar to our study as there was a positive correlation between CA125 levels and systolic and diastolic blood pressure, platelet count, urinary protein and serum uric acid levels.
CONCLUSION

This study has shown that serum CA125 is elevated in preeclamptic pregnancy as compared with normal pregnancy and even significantly higher in cases of severe preeclampsia therefore has potential as biomarker or prognosticator of disease severity. Larger studies with a larger sample size are however required in order to determine if CA125 is suitable as a biomarker for preeclampsia follow up as well as determine an acceptable cut off value for this marker.

LIMITATIONS OF THE STUDY

1. There is the possibility that some of the women with preeclampsia may be chronic hypertensive or diabetic patients but did not know and as such volunteer wrong information.

2. The overall cost of performing the study prevented a larger sample size from being used.
RECOMMENDATIONS

1. More work (multicentre studies involving a larger sample size and population) is needed to determine the appropriate clinical importance of CA125 in the management of preeclampsia.

2. Larger studies may help develop a threshold value for which management protocols to improve outcomes of pregnancies complicated by preeclampsia can be developed.
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PROFORMA

Initials: ………………………… Hospital Number:……………………

1. BIODATA

1.1 Age……………………………

1.2 Marital status 1.21. Married □ 1.22. Single □

1.23. Divorced □ 1.24. Widowed □

1.5 Educational status 1.51 No formal education □

1.52 Primary school □

1.53 Secondary school □

1.54 OND or other diploma □

1.55 HND/Bachelors or higher □

1.7 Occupation. 1.71. Professionals 1.72. Skilled non professionals

1.74. Unskilled/housewives

1.8 Social Class I II III IV V

1.8 booking Status booked Unbooked

2. OBSTETRIC HISTORY

2.1 Last menstrual period………………

2.2 Expected date of delivery…………

2.3 Gestational age: Calculated…………

2.4 Parity 0 1 2 3 4 ≥5

INDEX PREGNANCY

3.1 Blood Pressure………………………..mmHg

1.2 Proteinuria…………………………..g/L

1.3 Platelet count----------------------X 10^9/L
1.4 Serum Uric acid------------------µmol/L
1.5 Serum creatinine-----------------µmol/L
1.6 Serum Ca125---------------------IU/ml

3. FAMILY AND SOCIAL HISTORY

3.1 Family history of hypertension......... yes........ no........
   3.12 In mother: yes........ no........
   3.13 In father: yes........ no........

3.2 Previous history of pregnancy induced hypertension yes........ no........

3.3 Smoking.................. yes........ no........
   3.31 Number of sticks/day?..............

3.4 Drinks alcohol.................. yes........ no........
   3.41 Quantity?...............  

4. DELIVERY DETAILS

4.1 Sex............

4.2 Mode of delivery............
   Estimated fetal weight------------

4.3 Birth Weight............

4.4 Intrauterine growth restriction-----------------

4.5 Placenta weight -----------------------

4.6 Intrauterine fetal death....................

4.7 Neonatal ICU Admission............

4.8 Early Neonatal Death .................
PATIENT’S INFORMATION SHEET AND CONSENT FORM.

I, Dr Bankole of the Department of Obstetrics and Gynecology of the Lagos University Teaching Hospital (LUTH) Idi Araba, am conducting a study on the level of CA125 in the serum of patients with Preecclampsia who present at the Obstetrics and Gynecology unit of the Lagos University Teaching Hospital.

The Aim of the study is to determine the level and clinical importance of CA125 antigen in normal and preeclamptic pregnancies and thus determine if there is any relationship between the Cancer antigen 125 and pregnancies complicated by preeclampsia in order to determine if it can be used to predict the presence of the disease in patients.

The study will involve administering a questionnaire where the obstetric history, history of present pregnancy as well as family history of hypertension will be obtained. Details surrounding delivery will also be obtained. Finally 5mls of blood will be taken from the all that choose to participate in the study. This procedure involves a needle prick and may cause slight pain which is transient and last only during introduction of the needle to draw blood.

The information obtained will be treated with utmost confidentiality. Please note that participation is voluntary and tests are carried out at no cost to you the patient. Refusal to be recruited into the study will not affect your care in any way. I will be grateful if you consent to participate in this study. Thank you.

Patient’s name and signature:  
Researcher’s name and signature:  
Date:
INFORMED CONSENT FORM

I ................................................. voluntary consent to participate in the above named research study conducted by Dr Bankole Gbemisola of the Department of Obstetrics and Gyneacology, Lagos University Teaching Hospital (LUTH), Idi-Araba, Lagos.

I have been given the following information.

1. That the research is undertaken to compare serum levels of CA125 in preeclampsia and normal pregnancy.
2. That 5 millilitres of blood will be taken from me at the time of recruitment.
3. That my participation in this research will be at no cost to me or my family.
4. That I am not exposed to any risk by participating in this study.
5. That the information generated by this study is for research purposes only.
6. That the information received from me will be treated as private and confidential.
7. That I have the right to ask questions on any aspect of this study that is not clear to me before I participate.
8. That I am guaranteed the right to withdraw from the study at any time and this will not affect the care I will receive in the hospital.

.........................................................................................................................

Signature/thumbprint                                        Date
IWE GBIGBA ASE

Emi …………………………………. Fe kopa ninu ayewo to nlo laro ni LUTH Idi-Araba ti Dokita Bankole nse oludari re.

Mo de mo wipe.

- Ayewo to nlo lowo yi ni lati mo ibasepo loorin CA125 ati oloyun to ni ifunpa giga ati ito protein ati oloyun ti ko ni ifunpa giga.
- Bi sibi agba eje kan ni won ma gba fun ayewo yi.
- Ikopa mi ko ni na mi ni ara Kankan
- Ko si ewu kan si mi ninu ayewo yi
- Gbogbo idahun si beere yi wa fun ighese yi nikan.
- Gbogbo idahun si ibeere yi ni a o mu ni asiri
- Mo ni eto lati bere ohun kohun to ba ru mi loju
- Mo ni eto lati ma ko pa ni igba ki igba ti o ba wun mi.

_______________________
Ite wo si iwe

_______________________
Ojo
Emi Dokita Bankole ti eka to n mojuto ilera obinrin ati oyun ni ni ti Lagos University Teaching Hospital, Idi-Araba nse ayewo lori iye CA125 ninu eje awon oloyun to ni ifunpa giga ti o nwa fun itoju ni ile iwo san yi.

Koko igbese yi ni lati mo iye ati iwulo CA125 ninu oloyun to ni ifunpa giga ati eyi ti ko ni ifunpa giga ati lati mo boya ibasepo wa laarin CA125 ninu oloyun to ni ifunpa giga ati lilo re ninu ase pejuwe asisan naa.

Ibese yi yip ni lo iwe ibeere pele be kan ti yio wa beere iye oyun ti omobinrin na ti ni ati a ba jade re pelu eyi ti o wa ninu re ni nsise tele ati boya aarun ifunpa giga wa ninu idile omobinrin naa.

Paripari re, eje bi koju sibi kan lo la o gba lara omobinrin naa lati fi se ayewo na. Gbogbo idahun si ibeere wa la o mu ni oro asiri ati wipe, ayewo yi ko ni na yin ni owo kankan ti e ko ba fe kopa ninu ayewo, ko di itoju to ye ki e rigba ninu oyun ni ile iwo san yi.

**Oruko yin**                      **Oluko Oludari**

_____________________            ___________________

**Itewo si ika**                      **Itewo si ka**

_____________________            ___________________