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**Adegoke Bosede Oluwasayo**
Department of Chemical Pathology, Ekiti State University, Ado-Ekiti, Nigeria

**Atiba Adeniran Samuel**
Department of Chemical Pathology, Ekiti State University, Ado-Ekiti, Nigeria

**Adegoke Benjamin Olamide**
Department of Pharmacology and Therapeutic, College of Medicine, Ekiti State University, Ado-Ekiti, Ekiti State, Nigeria

**Abayomi Olawale Ayobami**
Department of Radiology, College of Medicine, Ekiti State University, Ado-Ekiti, Ekiti State, Nigeria

**Olofinbiyi Oluwafunke Rebecca**
Department of Nursing Science, College of Medicine, Ekiti State University, Ado-Ekiti, Ekiti State, Nigeria

**Abayomi Waheed**
School of Anaesthesia Studies, Badagry/General Hospital, Badagry, Nigeria

**Adewumi Oluwafemi Adebisi**
Department of Hospital Services, Federal Ministry of Health, Abuja, Nigeria

**Akadiri Olumide**
Department of Obstetrics and Gynaecology, University of Medical Science, Ondo, Ondo State, Nigeria

**Adeniyi Omotayo Oladele**
Bayly Family Practice and Walk in Clinic, Bayly Street, Toronto, Canada

**Olofinbiyi Babatunde Ajayi**
Department of Obstetrics and Gynaecology, College of Medicine, Ekiti State University, Ado-Ekiti, Ekiti State, Nigeria

**Corresponding Author:**
**Olofinbiyi Babatunde Ajayi**
Department of Obstetrics and Gynaecology, College of Medicine, Ekiti State University, Ado-Ekiti, Ekiti State, Nigeria

# Predictive value of vascular endothelial growth factor receptor-1 and lipid profile in pre-eclampsia

**Adegoke Bosede Oluwasayo, Atiba Adeniran Samuel, Adegoke Benjamin Olamide, Abayomi Olawale Ayobami, Olofinbiyi Oluwafunke Rebecca, Abayomi Waheed, Adewumi Oluwafemi Adebisi, Akadiri Olumide, Adeniyi Omotayo Oladele and Olofinbiyi Babatunde Ajayi**

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**Abstract**
**Introduction:** Preeclampsia, a complex hypertensive disorder occurring during pregnancy, poses significant risks to both maternal and fetal health. Vascular Endothelial Growth Factor Receptor-1 (VEGFR-1) and abnormal lipid profile have been implicated in the aetiopathophysiology.
**Materials and Methods:** Pre-eclamptic patients were enrolled in the study starting at the 20th week of gestation. The recruitment process took place at random between December 2021 and December 2022. As controls, apparently similar expectant mothers were chosen. Each participant's complete blood was obtained, and the serum was used for the laboratory analysis of VEGFR-1 and the lipid profile characteristics. The parameters of the lipid profile and vascular endothelial growth receptor-1 were measured using ready-to-use commercially produced kits based on the enzymatic and enzyme-linked immunosorbent assay (ELISA) techniques respectively. SPSS version 20 was used for data analysis. The threshold for statistical significance was established at 0.05.
**Results:** Individuals with pre-eclampsia had noticeably greater serum levels of VEGFR-1, LDL-c, TG, and TC than individuals in the control group ($p$<0.001). The median range of VEGFR-1(pg/ml) (1285, $p$<0.001), the mean TC (mmol/l) (6.23, $p$<0.001), TG (mmol/l) (2.75, $p$<0.001), and LDL-c (mmol/l) (3.69, $p$<0.001) were significantly raised among the pre-eclamptic women when compared to control except HDL-c (mmol/l) (1.36 $p$<0.001) which was lower in participants with pre-eclampsia. Plasma VEGFR-1 and the lipid profile parameters both had statistically significant levels of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).
**Conclusion:** Plasma VEGFR-1 and lipid profile characteristics may serve as reliable pre-eclampsia predictors.

**Keywords:** VEGFR-1, predictive value, lipid profile, preeclampsia

## Introduction

Preeclampsia, a complex hypertensive disorder occurring during pregnancy, poses significant risks to both maternal and fetal health [1]. It is associated with high maternal and perinatal morbidity and mortality; and one of the commonest causes of maternal deaths globally, accounting for about 15% of maternal mortality [2]. Prevalence ranging from 0.74-16.7% has been quoted globally [3, 4]. Although, Olowokere *et al*. recorded a relatively low prevalence rate of 1.9% at Ekiti State University Teaching Hospital (the place of the current study) [4], anecdotal reports show that preeclampsia is about the commonest obstetric challenge encountered at all levels of healthcare in the entire state.

It is essentially a development of high blood pressure and significant proteinuria after 20 weeks gestational age in a previously normotensive and non-proteinuric individual [5]. Preeclampsia is a disease of theories as the precise etiology remains elusive [6-8]. Theories advanced for the etiopathogenesis of preeclampsia include defective trophoblastic invasion, immune maladaptation, vascular abnormalities/defective vascular endothelial growth factor, abnormal lipid metabolism/oxidative stress and genetic factors; central to which is abnormal trophoblastic invasion theory [6]. Usually, a placenta trigger sets off the disease, which is then followed by a systemic reaction in the mother culminating in a life-threatening multisystemic disease associated with eclampsia, HELLP syndrome (hepatic dysfunction characterized by hemolysis [H], elevated liver enzymes [EL], and low platelets [LP]), acute kidney injury, pulmonary

oedema, placental abruption, coagulation disorder, intrauterine growth restriction, intrauterine foetal death, maternal death etc. [9].

Pre-eclampsia's genesis and pathophysiology have been extensively studied, yet there are still many unanswered questions. Some of these hypotheses include links between immune system alteration, trophoblastic invasion and processes of oxidative stress. Pre-eclampsia has been associated with defective vascular endothelial growth factor receptor 1 (VEGFR-1) and abnormal blood lipid profile. Vascular endothelial growth factor (VEGF) intricately influences the pathogenesis of preeclampsia. Dysregulation of VEGF, a pivotal angiogenic factor, disrupts normal vascular development, leading to endothelial dysfunction and impaired placental perfusion. In preeclampsia, decreased VEGF levels contribute to widespread vasoconstriction, endothelial injury and increased vascular permeability. These disruptions compromise maternal vascular integrity, manifesting as hypertension and multi-organ complications. Dyslipidemia emerges as a potential contributor to preeclampsia's intricate pathogenesis. Altered lipid metabolism, marked by elevated triglycerides and reduced high-density lipoprotein, may disrupt placental function and escalate oxidative stress. Exploring dyslipidemia's involvement enhances our understanding of preeclampsia, paving the way for targeted interventions to mitigate its impact on maternal and fetal health.

This study sought to explore the predictive value of VEGF-1 and blood lipid profile for preeclampsia in environment of study; this is with a view to contributing to the existing body of knowledge on the aetiopathogenesis of the disease, being one of the commonly encountered challenging obstetric condition not only in the environment of study but also in Nigeria. Understanding the nuanced roles of VEGF and dyslipidaemia in preeclampsia pathogenesis holds promise for targeted therapeutic interventions, aiming to restore vascular homeostasis and alleviate the profound impact on maternal and fetal health.

## Materials and Methods

It was a cross-sectional comparative research conducted at the departments of Obstetrics & Gynecology and Chemical Pathology of Ekiti State University Teaching Hospital, Ado-Ekiti. Ekiti State, a low resource setting in southwest Nigeria, is a homogenous state dominated by youths. It is located between latitudes 70 and 80 51 N and 40 451 E. It has a land area of 5,435 square kilometers and 2,398, 957 people, according to the 2006 census [10].

The study was conducted over a year period, December 2021 to December 2022. A total of 190 pregnant women were recruited for the study. One hundred and twenty (120) of these participants were diagnosed as having pre-eclampsia according to the criteria of the International Society for the Study of Hypertension in pregnancy (a systolic blood pressure of greater than or equal to 140 mmHg and/or diastolic blood pressure of greater than or equal to 90 mmHg for blood pressure taken at least 4 hours apart after the 20th week of gestation with significant proteinuria ≥ 300 mg / 24hours. The control participants recruited were 70 women who were age- and gestational age-matched, normotensive and non-proteinuric who visited the clinic at the same period. Pregnant women with chronic hypertension, urinary tract infection (UTI), renal pathology, diabetes mellitus, multiple gestation, malignancy, psoriasis and rheumatoid arthritis were excluded from the study.

About 4 milliliters of venous blood sample was collected from each participant into a plain specimen bottle after a 12-14 hour overnight fast. The blood sample was processed to extract serum which was used for the laboratory analyses of the required biochemical parameters. Total cholesterol (TC), Triglyceride (TG) and HDL-c were analyzed using ready to use kits manufactured by Fortress Diagnostics(R), United Kingdom [11]. Low density lipoprotein cholesterol (LDL- c) was calculated using Friedewald's formula [12]. Vascular endothelial growth factor receptor 1 (VEGFR1) was analyzed with another ready to use kits (ELISA) manufactured by Elabscience Biotechnology, with catalog number E-ELH1087 and lot number xx2JCJ2VTI, BWLU7XVFJ, D7HB9BYXH.

Ethical approval for study was obtained from the Research and Ethics Committee of Ekiti State University Teaching Hospital; protocol number being EKSUTH/A67/2019/09/015.

### Statistical Analysis

The data collected were analyzed using descriptive and inferential statistics using Statistical Package for Social Statistics (SPSS), version 20.0. Chi-square was used for categorical variables. Sensitivity, specificity, positive predictive value, negative predictive value and area under curve (AUC) were determined by plotting Receiver Operating Characteristic curve (ROC curve). The degree of correlation of data was determined by Spearman's correlation analysis. The results were expressed as mean ± 2SD. A p- value of ≤ 0.05 was taken as significant.

## Results

Table 1 shows the socio-demographic distributions of the participants. There was no statistically significant difference in the mean age of the preeclamptics (31.32±4.66) compared to the control group (31.09±5.02). While the incidence of preeclampsia was highest in 25-34 year age bracket (68.3%), it was lowest in 18-24 year age bracket (67.7%). Married women accounted for the larger percentage of the patients that developed preeclampsia (95%) compared to singleton women (5%). Type of occupation was significantly associated with development of preeclampsia (< 0.005) with artisans carrying the largest percentage (38.3%)

**Table 1:** Socio-demographic distribution of participants

| Parameter | Preeclampsia N=120 (%) | Normotensive N=70 (%) | $\chi^2$ | P-Value |
|---|---|---|---|---|
| **Age (yr)** | 31.32±4.66* | 31.09±5.02* | -1.192-1.654¥ | 0.749 |
| **Age groups** | | | | |
| 18-24yr | 8(6.7) | 6(8.6) | 0.405 | 0.817 |
| 25-34yr | 82(68.3) | 45(64.3) | | |
| 35-44yr | 30(25) | 19(27.1) | | |
| **Marital status** | | | | |
| Single | 6(5) | 2(2.9) | 0.503 | 0.478 |
| Married | 114(95) | 68(97.1) | | |
| **Tribe** | | | | |
| Yoruba | 105(87.5) | 66(94.3) | 4.373 | 0.112 |
| Igbo | 8(6.7) | 4(5.7) | | |

| | | | | |
|---|---|---|---|---|
| Hausa | 7(5.8) | 0 | | |
| **Educational status** | | | | |
| None | 3(2.5) | 0 | 3.484 | 0.323 |
| Primary | 1(0.8) | 2(2.9) | | |
| Secondary | 33(27.5) | 23(32.9) | | |
| Tertiary | 83(69.2) | 45(64.3) | | |
| **Occupation** | | | | |
| Self-employed | 27(22.5) | 13(18.6) | 14.896 | < 0.005** |
| Government employed | 12(10) | 17(24.3) | | |
| Private employed | 17(14.2) | 7(10) | | |
| Artisan | 18(15) | 19(27.1) | | |
| Trading | 46(38.3) | 14(20) | | |
| **Religion** | | | | |
| Christianity | 99(82.5) | 60(85.7) | 0.335 | 0.563 |
| Islam | 21(17.5) | 10(14.3) | | |

As shown in table 2 below, serum VEGFR-1, Tg, LDL-c and TC levels were significantly higher, and HDL-c levels were found to be considerably lower (p=0.017) in participants with pre-eclampsia as compared with the control participants.

**Table 2:** Biochemical parameters of the participants

| Parameter | Preeclampsia (Mean ± SD) N=120 | Normotensive (Mean ± SD) N=70 | CI | P-Value |
|---|---|---|---|---|
| VEGFR-1 (pg/ml) | 1285(1145.5-1292)[b] | 869.5(858-936.3)[b] | Missing | < 0.001[U]** |
| TC (mmol/l) | 6.23±0.90 | 4.72±0.59 | 1.30-1.72 | 0.001** |
| TG (mmol/l) | 2.75±0.49 | 1.70±0.36 | 0.93-1.17 | 0.004** |
| HDL-c (mmol/l) | 1.36±0.25 | 1.50±0.35 | -0.233-(-0.05) | < 0.001** |
| LDL-c (mmol/l) | 3.69±0.88 | 2.47±0.60 | 1.01-1.43 | 0.003** |

B represents median (interquartile range)
U represents Mann-Whitney U test

The clinical characteristics and laboratory data of the study and control groups are summarized in Table 3. Receiver Operating Characteristic Curve (ROC) analysis was performed to determine the sensitivity and specificity. Using a cut-off concentration of 1135 pg/ml, VEGFR-1 has sensitivity and specificity of 80.3% and 66.7% respectively. The positive predictive value and negative predictive value were 61.6% and 83.5% respectively. Using cut-off concentration of 2.29 mmol/l, triglyceride (TG) had sensitivity and specificity of 85.5% and 84% respectively. Positive predictive value and negative predictive values were 61.3% and 86.9% respectively. Other biochemical parameters measured are as shown in table 3.

**Table 3:** Diagnostic Performance of the Parameters among the Study Participants

| Laboratory parameter | TP | FP | FN | TN | Sensitivity | Specificity | PPV | NPV |
|---|---|---|---|---|---|---|---|---|
| VEGFR-1 (pg/ml) | 61 | 38 | 15 | 76 | 80.3 | 66.7 | 61.6 | 83.5 |
| TC (mmol/l) | 65 | 36 | 11 | 78 | 85.5 | 68.4 | 64.4 | 87.6 |
| TG (mmol/l) | 65 | 41 | 11 | 73 | 85.5 | 64 | 61.3 | 86.9 |
| HDL-c (mmol/l) | 42 | 79 | 34 | 35 | 55.3 | 30.7 | 34.7 | 50.7 |
| LDL-c (mmol/l) | 63 | 41 | 13 | 73 | 82.9 | 64 | 60.6 | 84.9 |

TP True positive FP False positive
FN False negative TN True negative
PPV Positive predictive value NPV Negative predictive value

Table 4 shows proteinuria among the pre-eclamptic women had a negative correlation (r=-0.253) with VEGFR-1 which was significant ($p$<0.05). Similarly, proteinuria correlated negatively with serum HDL-c concentration, this was however not significant. Positive correlations were found between the degree of proteinuria and TG, TC, and LDL-c. However, it was only LDL-c that had a significant (p=0.003) correlation (r = 0.198) with proteinuria,

**Table 4:** Bivariate correlation of the level of serum biochemical parameters with the degree of proteinuria in the participants with preeclampsia

| | Spearman correlation | P-Value |
|---|---|---|
| VEGFR-1 (pg/ml) | -0.253 | **0.005 ** ** |
| TC (mmol/l) | 0.143 | 0.118 |
| TG (mmol/l) | 0.1 | 0.279 |
| HDL-c (mmol/l) | -0.136 | 0.139 |
| LDL-c (mmol/l) | 0.198 | 0.003 ** |

**p-value is significant

The degree of blood pressure among the pre-eclamptic women had a negative correlation with (r = -0.247) VEGFR-1 which was statistically significant (p=0.07). Similarly, raised blood pressure correlated negatively with HDL-c which was statistically significant (table 5). In the same vein, positive correlation found between raised blood pressure and TG, TC, LDL-c. HDL-c was negatively correlated (r = -0.233) with blood pressure (table 5)

**Table 5:** Bivariate correlation of the level of serum parameters with the severity of blood pressure in the participants with preeclampsia

| | Spearman correlation | P-Value |
|---|---|---|
| VEGFR-1(pg/ml) | -0.247 | 0.007** |
| TC (mmol/l) | 0.074 | 0.420 |
| TG (mmol/l) | 0.043 | 0.642 |
| HDL-c (mmol/l) | -0.233 | 0.01** |
| LDL-c (mmol/l) | 0.123 | 0.181 |

**p-value is significant

## Discussion

Pre-eclamptic women in this study had a median VEGFR-1 range that was noticeably higher than the control group. A study by Hirashima *et al*. found a similar result [13]. Pre-eclamptic women were shown to have greater levels of the lipids (TC, TG, and LDL-c) than the control group. Pre-eclamptic women's high density lipoprotein (HDL-c) levels were lower than those of the control group. These findings were consistent with that of Adiga *et al*., who found that pre-eclamptic women's lipid profiles were considerably greater than those of the normotensive control group [14]. Additionally, Tesfa *et al*. revealed in a meta-analysis that the risk of pre-eclampsia was strongly correlated with the maternal serum lipid profile [15].

According to this study, pre-eclamptic women had higher levels of VEGFR-1 than women who did not have the disease. Although not exactly the same in magnitude (slightly higher), the present study's results of sensitivity, specificity, positive predictive value and negative predictive value followed the same pattern as Salk *et al*.'s study [16]. Likewise, Chaiworapongsa *et al.* predicted early onset preeclampsia with VEFGR-1 concentrations in early pregnancy and mid-trimester of sensitivity of 100% and specificity of 98-99% [17]. Differences in magnitude may be explained by differences in study design and study participants' selection methods. While the present study adopted a comparative study design, Salk *et al.* adopted a nested case-control design where one hundred and forty-six pregnant women with normal blood pressure previously were prospectively included in the study [16]. Chaiworapongsa *et al.* used delivery outcomes to classify their participants. Generally, striking similarities were found in order of values [17] low levels of HDL-c may compromise the function of all these processes. In this study, women with pre-eclampsia were found to have significantly deceased levels of HDL-c than the control. This is in consonance with the results of other previous studies [14, 18]. In a study conducted among Portuguese women, those with pre-eclampsia had a lower HDL-c level compared with healthy pregnant women [19].

In the present study, there was a statistically significant negative correlation between proteinuria and VEGFR-1, and a significant positive correlation between proteinuria and LDL-c. This implies that LDL-c could also be used in the diagnosis or monitoring of pre-eclampsia. However, this has to be validated by further studies. The current study also showed a significant negative between elevated blood pressure and VEGFR-1. This implies that as blood pressure increased, VEGFR-1 would show a decrease or vice versa. Also, the study found a significant negative or inverse correlation between elevated blood pressure and HDL-c. This finding agrees with that of Tesfa *et al.* where the serum HDL-c level was lower in pre-eclamptic women compared to the controls [14]. The control group had normal blood pressure and relatively higher HDL-c while the pre-eclamptic women had raised blood pressure and relatively lower HDL-c. However, other variables were not statistically significant and there was no correlation between VEGFR-1, HDL-c and raised blood pressure.

The result from this study showed that there was a significant difference in VEGFR-1 and lipid profile in pre-eclamptic participants compared to normotensive protein free participants. Pre-eclamptic patients in this study had significantly higher serum level of TG compared to the controls which is consistent with the findings of previous studies [20, 21]. In these studies, women with pre-eclampsia had a marked increase in serum TG and this may be referred to as TG-related vasculopathy which may be one of the possible etiopathogenesis of pre-eclampsia [22].

The higher levels of circulating serum TG observed in women with pre-eclampsia may be further explained as an essential step in lipid-mediated endothelial dysfunction. However, the mechanisms driving the abnormal elevation, and ultimately pre-eclampsia are unclear [22]. During pregnancy, there is an increase in the hepatic lipase activity and decrease in lipoprotein lipase activity. Hepatic lipase is responsible for the increased synthesis of the triglycerides at the hepatic level, and the decreased activity of lipoprotein lipase may be responsible for the decreased catabolism at the adipose tissue level [22].

The total cholesterol in pre-eclamptic women was also observed to be significantly higher than in normotensive women in this study. This is in keeping with the findings of Adiga *et al.* who reported significantly elevated TC in pre-eclamptic patients compared to normal pregnant women [14]. They concluded that hypercholesterolemia could lead to excessive lipid peroxidation culminating in an imbalance between peroxidases and antioxidants, which in turn resulted in oxidative stress; oxidative stress has been postulated to be linked to the pathogenesis of pre-eclampsia [23].

Uzun *et al.* observed that serum concentrations of lipid parameters (including total cholesterol) were significantly higher in pre-eclampsia compared with normotensive pregnancy [24]. Their findings suggested that oxidative stress, dyslipidemia and decreased paraoxonase activities may cause vascular endothelial damage and contribute to the pathophysiology of pre-eclampsia [24]. On the contrary, Punthumapol *et al.* and Siddiqui *et al.* found no statistically significant difference in the level of cholesterol in pre-eclamptics compared to apparently healthy pregnant women [25, 26].

However, serial maternal serum measurements of measured biochemical parameters, including measurements in the first and second trimesters, were not performed in this current study, thus limiting it. This would have given more information on the trend of these parameters in the course of the pregnancy.

In conclusion, this study showed that TC, TG, LDL-c, HDL-c and VEGFR-1 could be reliable biomarkers that to screen for or predict pre-eclampsia. They have statistically significant mean difference, high specificity, sensitivity, positive predictive value and negative predictive value.

## Conflict of Interest

Not available

## Financial Support

Not available

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