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Activated Protein C Resistance in Patients with Pre-Eclampsia in Lagos, Nigeria

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Abstract

Background: Preeclampsia is reported to complicate 2% - 8% of pregnancies globally and is an important cause of maternal and perinatal morbidity and mortality. The aetiology and pathogenesis are still poorly understood and substantial improvement has not been made in the prediction, prevention and treatment of the disease. **Objective**: To compare the frequency of activated protein C resistance (APC-R) in patients with pre-eclampsia to that of normotensive pregnant women and to determine the correlation between activated protein ratio (APC-ratio) and the severity of pre-eclampsia. **Methodology**: A cross-sectional study was carried out in 100 pre-eclamptic patients and 100 normotensive pregnant controls. The APC-ratio was determined using the modified activated partial thromboplastin time. Study participants with APC-ratio of less than 2.0 were defined as having APC-R. Data was analyzed using SPSS version 22.0. **Results:** Mean APC-ratio was significantly lower in pre-eclamptics (2.89 ± 1.70) compared to normotensive pregnant women (3.57 ± 1.06) ($p = 0.0008$) and the levels were also higher in mild (2.95 ± 1.15) compared to severe pre-eclamptics (2.62 ± 1.14). The frequency of APC-R was 26% among women with pre-eclampsia compared to 4% among normotensive controls ($p = 0.000$). Among 100 pre-eclamptic women 7 (21.2%) out of 33 with mild pre–eclampsia had APC-R, while 19 (28.4%) out of 67 with severe pre-eclampsia had APC-R. APC-ratio had a significant negative correlation with mean arterial blood pressure ($r = -0.324$; $p = 0.000$) and proteinuria ($r = -0.379$; $p = 0.000$) among study participants. **Conclusion**: The frequency of activated protein c resistance is significantly higher in pre-eclamptics compared to normotensive pregnant women and this is more pronounced in those with severe pre-eclampsia compared with those with

mild disease. APC-R may therefore be used as a marker of severity in the disease.

Keywords

Activated Protein C Resistance, Activated Protein C Ratio, Pre-Eclampsia

1. Introduction

Preeclampsia is a life threatening multi-systemic disorder of uncertain origin unique to human pregnancy. It is commonly defined as hypertensive disorder of pregnancy characterised by the presence of new onset hypertension coupled with new onset proteinuria both usually occurring after 20 weeks gestation [1] [2]. The disease is so named as the precursor to eclampsia, wherein the woman experiences new onset generalised grand mal seizures as the prototypical severe manifestation.

Preeclampsia is reported to complicate 2% - 8% of pregnancies globally and is an important cause of maternal and perinatal morbidity and mortality [3] [4]. In Nigeria, the incidence of preeclampsia varies between 4% and 17% and is listed as one of the top three causes of maternal death contributing between 11% and 46.4% [5]-[10].

Despite extensive research into the subject area, the aetiology and pathogenesis is still poorly understood and substantial improvement has not been made in the prediction, prevention and treatment of the disease. Extensive research has suggested that preeclampsia is associated with intervillous and spiral artery thrombosis, vascular endothelial damage and abnormalities of coagulation leading to inadequate maternal, foetal and placental circulation [11].

During normal implantation, trophoblasts invade the decidualized endometrium, leading to spiral artery remodeling and obliteration of the tunica media of myometrial spiral arteries, allowing increased blood flow to the placenta, all independent of maternal vasomotor changes [12]. In preeclampsia, trophoblasts fail to adopt an endothelial phenotype, which leads to impaired trophoblast invasion and incomplete spiral artery remodeling. The resultant placental ischemia leads to an increase in angiogenic markers [12]. The two most studied and implicated biomarkers, especially in relation to the development of preeclampsia, are soluble FMS-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) [12] [13]. sFlt-1 is an anti-angiogenic factor that inhibits neovascularization. Higher levels of sFlt-1 are found in patients with preeclampsia and the placentas of patients with preeclampsia. The levels of PlGF are lower, and the ratio between sFlt-1 and PlGF is elevated in patients with preeclampsia. sFlt-1 binds to and decreases levels of vascular endothelial growth factor (VEGF) and placental growth factor, which are important mediators of endothelial cell function [12] [13].

The vascular endothelial dysfunction and thrombotic component of preeclampsia suggest that aberrations in the clotting cascade may be contributory and in the past few years, attention has been focused on the roles that thrombophilia may play in the pathogenesis of preeclampsia [14] [15] [16].

Thrombophilia is commonly defined as a tendency for intravascular clotting [17]. They are inherited or acquired conditions that predispose affected individuals to thromboembolism. Deficiencies of antithrombin III, protein C or protein S are rare, each found in about 3% of patients with thrombosis [18]. Factor V Leiden, factor II G20210, lupus anti-coagulant and hyperhomocysteinaemia are other conditions associated with thrombophilia [18] [19]. Growing evidence suggest that thrombophilia is associated with venous thromboembolism and adverse pregnancy outcomes, such as foetal loss, intrauterine growth restriction, placental abruption, recurrent miscarriage, unexplained still birth and preeclampsia [16] [20].

Dahlback and Hildebrand described a hereditary abnormality in anticoagulant system termed activated protein C resistance (APC-R) [21]. Bertina *et al.* demonstrated that most causes of APC-R are associated with the presence of a G to A substitution at the nucleotide position 1691 in the factor V gene [22]. The resulting factor V molecule (factor V Leiden, (FVL) has arginine at position 506 replaced by glutamine, the cleavage site for APC, thereby giving rise to APC-R [23].

Recent studies have shown that heterozygous carrier rate of the Leiden mutation depends on ethnic origin. The carrier rate ranges from about 15% - 20% in Scandinavian countries to an overall rate of about 4.4% in other European countries [24] [25]. Data for Africa is sparse, but a recent study in Lagos, Nigeria reported a prevalence rate of 2% for APC-R [26].

The potential role of factor V Leiden and APC-R in the development of preeclampsia has been extensively studied but most results are conflicting [27]-[36]. Furthermore, most of the research in this area have been carried out in the white population. Very little data are available in the African population. A recent report from South Africa however failed to demonstrate any association between factor V Leiden and preeclampsia [36]. Extensive search of the literature did not reveal any such study in Nigeria. This necessitates the need for establishing what constitutes normal physiology or may contribute to pathophysiology of the disease process in our own population.

This study was designed to examine the association between preeclampsia and APC-R and to determine whether APC-Ratio correlates with the severity of the disease in Lagos, Nigeria.

2. Materials and Methods

2.1. Study Site

The study was carried out among pregnant women attending the antenatal clinic or admitted into lying-in wards of the maternity unit of the Department of Ob-

stetrics and Gynaecology, Lagos University Teaching Hospital, Idi-Araba, Lagos in the South-western part of Nigeria. The study site accommodates a heterogenous population of antenatal patients of different socio-economic strata and ethnicity that could be representative of a typical Nigerian obstetric population.

2.2. Study Design

The study was a cross sectional study which involved pregnant women with pre-eclampsia as the study group and age-matched healthy pregnant women without pre-eclampsia, as controls.

2.3. Sample Size Determination

The women were divided into 2 groups—(A) apparently healthy normotensive pregnant women and (B) patients with pre-eclampsia/eclampsia. The sample size was calculated using Leslie Fisher's formula [37]

$$N = (Z\alpha + Z\beta)^2(P_o(1 - P_0) + P_1(1 - P_1)^2/(P_1 - P_0)^2,$$

where:

N = required minimum sample size in each group.

$Z\alpha$ = % of normal distribution corresponding to the required significant level of 5% = 1.96.

$Z\beta$ = point of normal distribution corresponding to the statistical power of 80% = 0.842.

P_o = response in the first group from previous study = 0.90.

P_1 = expected response in the second group = 0.80.

$N = (1.96 + 0.842)^2(0.8(1 - 0.8) + 0.90(1.0 - 0.90)^2/(0.9 - 0.8)^2$.

We obtained a minimum sample size of 49 in each group. We however projected a sample size of 100 for each group.

2.4. Sampling Technique

A conveniencje sampling method was used. Patients were recruited as they presented and gave consent until the desired sample size was attained.

2.5. Patients Selection

Pregnant women with pre-eclampsia were selected as cases, while normotensive pregnant women at onset of labour were selected as controls. All pregnant women with other medical conditions that may have additional effects on the coagulation system in pregnancy such as multiple pregnancy, pre-existing chronic hypertension, diabetes mellitus, preexisting renal, liver or peripheral vascular diseases were excluded from the study.

2.6. Definitions

Pre-eclampsia was defined according to the International Society for the Study of Hypertension (ISSHP) criteria as systolic blood pressure of 140 mmHg or higher and diastolic blood pressure of 90 mmhg or higher, on two occasions at

least four hours apart, occurring after the 20th week of gestation, or a single recording of diastolic blood pressure of 110 mmHg or more, in association with proteinuria of 2+ or more by dipstick testing or proteinuria of 1+ if the specific gravity of the urine is less than 1.030.

Severe pre-eclampsia was defined as blood pressure of 160/110 mmHg or higher, with urine dipstick showing 3+ or 4+ proteinuria in a random urine sample, or other evidence of severe disease like elevated serum creatinine, pulmonary oedema, oliguria (urine output < 500 mls in 24 hours), oligohydramnios, fetal growth restriction, HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) or symptoms of significant end organ involvement (like cerebral or visual involvement, epigastric or right upper quadrant pain). Women who met the criteria for pre-eclampsia but not for severe pre-eclampsia were categorized as having mild pre-eclampsia.

Eclampsia was defined as new onset generalised grand mal seizures in patients with pre-eclampsia.

Mean Arterial Blood Pressure (MABP) was calculated using the formula: 1/3[SBP + 2(DBP)], where SBP and DBP are the systolic and diastolic blood pressures respectively.

Body mass index (BMI) was calculated as weight in kilograms (at sampling) divided by the square of the height in metres.

2.7. Data and Sample Collection and Processing

Patients with preeclampsia diagnosed in the antenatal clinics, lying in wards, labour room and emergency units in the second and third trimester were recruited as cases while normotensive pregnant women matched for age, parity and gestational age in the labour ward were recruited as controls. Gestational age of pregnancy was calculated from the last menstrual period (LMP) or determined by ultrasonography done in early pregnancy where LMP was not known.

After consent was taken, the arterial blood pressure was measured in the brachial artery using a simple mercury sphygmomanometer, on the right arm in a comfortable sitting position, after ten minutes of rest. Urine samples were collected into a plain bottle and tested using urinary dip strip, the colour change was then compared to determine the urinary protein level and recorded as 0, 1+, 2+, 3+ or 4+ proteinuria.

A proforma was used to obtain information on each participant including demographic data, medical history, family history and examination findings at diagnosis.

Nine volumes (4.5 mls) of venous blood were collected by venepuncture into vacuum tubes containing 1 volume (0.5 ml) of 3.2% sodium citrate. This was then transported to the laboratory on ice. The blood sample was gently mixed and centrifuged at 1500G for 15 minutes to get platelet poor plasma. The plasma was then aliquot and stored at −70˚C pending batch analysis which was carried out within 2 weeks.

Prior to testing, all the samples were thawed at 37˚C in a water bath and test carried out within one hour. Prothrombin time test (PT), activated partial thromboplastin time (APTT), and a functional activated protein C resistance test (Activated protein C ratio) were measured using a sysmex semi-automated coagulation analyzer, model CA-101.

2.8. Test Procedure: Functional Activated Protein C Resistance Test

The procedure involved the use of modified activated partial thromboplastin time (APTT) based test in which a pre-dilution of patient plasma with factor V-deficient is made before assay with and without the addition of exogenous activated protein C. APC inactivates factor Va and factor VIIIa thus prolongs the clotting time in contrast to sample with factor V mutation, in which the prolongation is less.

APTT based assay of Activated protein C activity was measured using commercial assay kit; (Coatest APC Resistance V823120 manufactured by chromogenic instrument Laboratory Company, Lexigington MA USA and marked by (diapham Group) was used to determine the APC-Ratio hence the presence of AP C resistance in the participant. Each study participant's plasma was pre-diluted as 1 part patient plasma + 4 parts factor V deficient Plasma and incubated with APTT reagent for 5 mins. Coagulation was then triggered with the addition of calcium chloridein the presence and absence of exogenous APC.

APC-ratio was then calculated as APTT with APC activator/APTT without APC activator.

APC Resistance due to Factor V mutation was indicated when APC-ratio is below the cut-off value determine from calibration.

2.9. Determining the Cut-Off Value for APC-Ratio That Indicates Activated Protein C Resistance (APC-R)

As recommended by the kit manufacturer, the cut-off of the APC-ratio that determines APC-R should be established using the median APC-ratio of at least 30 plasma samples from apparently healthy individuals with age ranging between 20 - 65 years. In this study the median APC-Ratio of 100 apparently healthy subjects whose ages ranges between 28 - 35 years was used. APC-R cut off value is a product of the median APC-Ratio and 0.57.

The median APC-Ratio was 3.51. The cut-off value thus established is 3.51 times 0.57 equal 2.0. Therefore, participants with APC-Ratio less than 2.0 were regarded as having activated Protein C resistance.

2.10. Data Processing and Statistical Analysis

The data obtained was entered into the computer and analyzed using the statistical software package for Social Sciences (SPSS), version 22. Descriptive statistics (frequencies, means and standard deviation) were generated. Comparison between continuous variables was done using the student's t-test or ANOVA as

appropriate. Categorical variables were compared using the Chi square test with Yates correction or the Fisher test as appropriate. Correlation was determined using the Pearson's correlation co-efficient. A *p*-value less than 0.05 was statistically significant.

3. Results

One hundred normotensive pregnant women and 100 women with pre-eclampsia were enrolled into the study. Of the 100 participants with pre-eclampsia, 33 had mild pre-eclampsia, while 67 had severe pre-eclampsia as per definitions.

The socio-demographic characteristics of the study participants are shown in Table 1. There was no significant difference in the socio-demographics in the two groups, except for the booking status which showed a significantly higher percentage of un-booked patients in the pre-eclamptic group compared to controls ($P < 0.0001$).

Table 1. Socio-demographic characteristics of study participants.

	Pre-eclampsia (n = 100)	**Normotensive (n = 100)**	**P-value**
Mean age ± SD (years)	32.26 ± 5.64	31.50 ± 5.29	0.3272[i]
Median age years (IQR)	32 (28 - 36)	32 (28 - 35)	
Age range in years	19 - 44	18 - 43	
Occupation			
Low income	38	27	
Middle income	47	46	
High income	15	27	0.0706*
Education			
None	2	0	
Primary	10	8	
Secondary	32	38	
Tertiary	56	54	0.4280*
Tribe			
Hausa	5	6	
Igbo	30	37	
Yoruba	60	52	
Others	5	5	0.7070*
Booking Status			
Booked	55	86	
Unbooked	45	14	0.0000*
Religion			
Christianity	75	81	
Islam	25	19	0.3065*

i = student t test; * = Chi square test.

The clinical characteristics of women with pre-eclampsia compared to the normotensive controls are summarized in Table 2. Statistically significant differences were noted in the gestational age at delivery, the systolic, diastolic, and mean arterial blood pressures. There was no statistically significant difference in the body mass index between the two groups.

Table 3 shows the mean APC ratio and frequency of APC resistance between women with pre-eclampsia and normotensive control participants. The mean APC ratio was significantly lower in women with pre-eclampsia compared to normotensive ($P = 0.0008$). Twenty six percent of the women with pre-eclampsia had APC resistance compared to 4% of the normotensive pregnant women controls. This difference was statistically significant ($P = 0.0000$).

Table 4 shows the mean APC ratio in normotensive controls, women with mild pre-eclampsia and women with severe pre-eclampsia. Statistically significant differences were observed between the three groups. APC ratios were significantly lower in women with severe pre-eclampsia compared to women with mild pre-eclampsia which in turn is lower than normotensive controls.

Table 2. Clinical characteristics of study participant.

	Pre-eclampsia n = 100	Normotensive n = 100	*P* value
Gestational age (weeks) ± SD	33.95 ± 4.89	38.75 ± 2.44	0.0000
Body mass index (kg/m^2) ± SD	29.78 ± 4.34	28.20 ± 6.50	0.0500
Systolic blood pressure ± SD	165.30 ± 21.20	113.95 ± 13.01	0.0000
Diastolic blood pressure ± SD	104.86 ± 15.44	71.57 ± 10.63	0.0000
Mean arterial blood pressure ± SD	124.93 ± 15.25	85.71 ± 10.47	0.0000

Table 3. APC-ratio and frequency of APC Resistance between participant with pre-eclampsia and normotensive controls.

	Pre-eclampsia (n = 100)	Normotensive (n = 100)	*P*-value
Mean APC-ratio ± SD	2.89 ± 1.70	3.57 ± 1.60	0.0008[i]
APC resistance (APC ratio < 2.0)			
Yes	26	4	
No	74	96	0.0000*

i = student t test; * = Chi square test.

Table 4. Comparison of APC-ratio among normotensive, mild pre-eclampsia and severe pre-eclampsia study participants.

Categories	Mean APC-ratio ± SD	Median	Range
Normotensive (n = 100)	3.57 ± 1.06	3.51	0.86 - 7.00
Mild PE (n = 33)	2.95 ± 1.15	3.04	0.98 - 6.94
Severe PE (n = 67)	2.62 ± 1.14	2.67	0.13 - 5.61

F statistics = 18.68 (ANOVA), *p* value = 0.0000.

Table 5 shows the frequency of APC resistance in normotensive, women with mild pre-eclampsia and those with severe pre-eclampsia. Statistically significant differences were observed in the three groups. The percentage of APC resistance was significantly higher in participant with severe pre-eclampsia compared to mild pre-eclampsia which was in turn higher than normotensive controls.

Figure 1 shows a scatter plot of APC ratio and mean arterial blood pressure among study participants. There is a weak but statistically significant negative correlation (r = −0.324) between APC ratio and mean arterial blood pressure.

Figure 2 shows the scatter plot of APC ratio and the degree of proteinuria in the study participant. There is a weak but statistically significant negative correlation between APC ratio and degree of proteinuria.

4. Discussion

The vascular endothelial dysfunction and thrombotic component of pre-eclampsia suggests that aberrations in the clotting cascade may be contributory, and in the past few years, attention has been focused on the roles that thrombophilia may

Table 5. Frequency of APC resistance among categories of study participants.

	APC Resistance	
Categories	Yes (%)	No (%)
Normotensive (n = 100)	4 (4)	96 (96)
Mild Preeclampsia (n = 33)	7 (21.2)	26 (78.8)
Severe Preeclampsia (n = 67)	19 (28.4)	48 (71.6)

Chi Square = 19.87, DF = 2, *P* value = 0.0000.

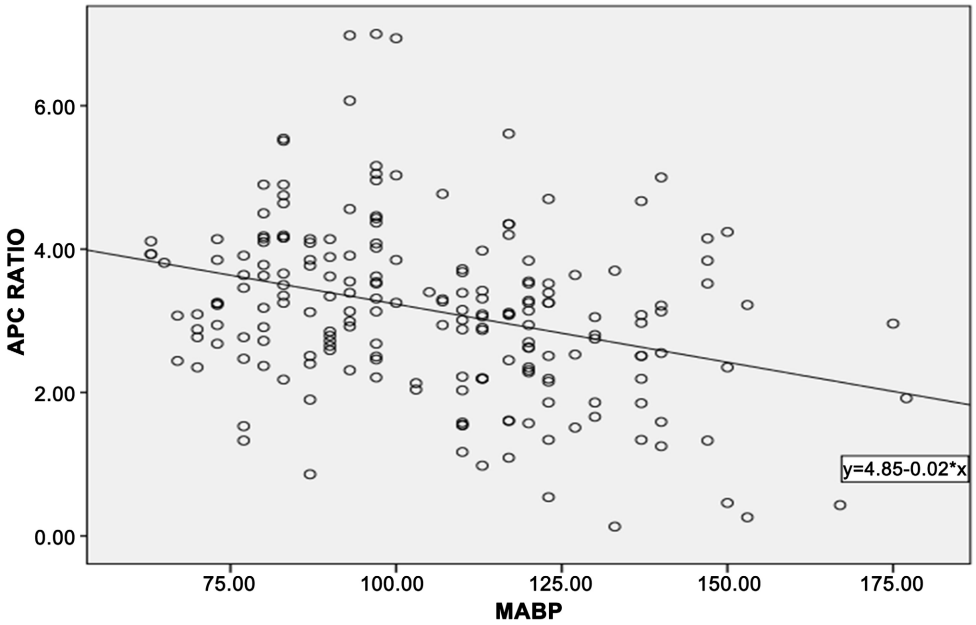

Figure 1. Scatter plot of APC ratio versus mean arterial blood pressure among study participants. Pearson's correlation co-efficient, r = −0.324, (p = 0.000).

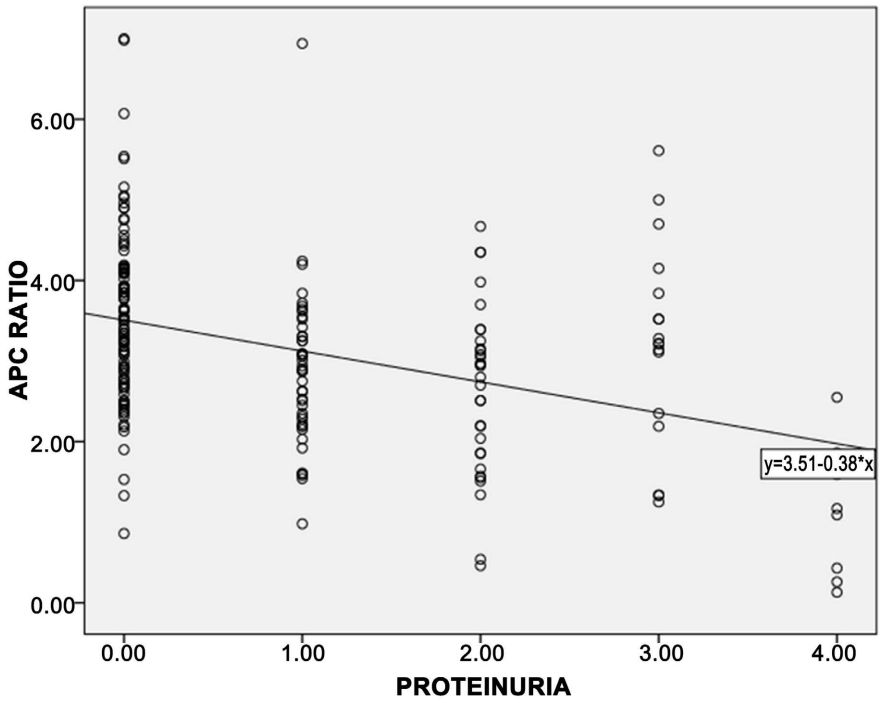

Figure 2. Scatter plot of APC ratio versus degree of proteinuria among study participants. Pearson's co-efficient of correlation was r = −0.379 (p = 0.000).

play in the pathogenesis of pre-eclampsia [14] [15] [16]. One of the most extensively studied thrombophilia thought to play a role in the pathogenesis of pre-eclampsia is the activated protein C resistance.

There have been conflicting reports on the relationship between activated protein C resistance and pre-eclampsia, with some studies showing association while some others failed to demonstrate any association. This study was carried out to investigate the association between activated protein C resistance and pre-eclampsia in a black obstetric population and the possibility of activated protein C ratio being used as a marker of severity of pre-eclampsia.

This study did not show any significant difference with respect to the socio-demographic characteristics of the patients with pre-eclampsia and controls except with respect to the booking status of the patients. More un-booked patients were found in the women with pre-eclampsia, and this is because the study was carried out in a tertiary institution which is a referral centre for pregnancies that are already complicated.

This study demonstrated a lower APC ratio in patients with pre-eclampsia than normotensive pregnant women and a higher percentage of APC resistance of 26% compared to only 4% in the normotensive pregnant women. This finding is similar to that reported by Paternoster el from Padova, Italy [28]. The higher percentage of APC resistance is however lower than the 2% prevalence reported from a study involving the general population in Nigeria [26].

This higher prevalence of APC-resistance in the participants with pre-eclampsia may be due to decrease in the plasma level of coagulation inhibitors and the in-

crease in coagulation factors resulting in endothelial damage and coagulation cascade activation [38]

This higher prevalence of APC-resistance in the participant with pre-eclampsia suggests that APC resistance may be associated with the pathogenesis of pre-eclampsia. It may also indicate a higher incidence of the acquired form of APC-resistance or inherited form (factor V Leiden). Placental infarctions and micro-embolisms are considered to be the principal pathophysiological changes in preeclampsia. This study suggests that APC resistance with a predisposition to thromboembolism is a risk factor for preeclampsia.

Several studies have also demonstrated an association between pre-eclampsia and APC resistance/factor V Leiden. In a meta-analysis of cohort studies, Dudding *et al.*, reported that maternal factor V Leiden (inherited form of APC-R) appears to increase the risk of pre-eclampsia by almost 50% [31]. Also, Kosmas *et al.* assessed 19 studies that have evaluated this association and concluded that women with the factor V Leiden have a 2.5-fold risk of developing pre-eclampsia compared to pregnant women without the mutation [39]. A recent nested case control study which assessed 198 pregnant Iranian women with pre-eclampsia compared with 201 healthy pregnant women as controls found that the prevalence of factor V Leiden and APC-R to be 8.6% in cases and 1% in controls [30].

Paternoster *et al.* assessed 35 normotensive pregnant women and 47 women with preeclampsia and demonstrated a greater reduction in activated protein C ratio in participants with pre-eclampsia compared to controls in Italian women [14]. In this study, more participants with pre-eclampsia compared to Paternoster *et al.* were assessed which also shows lower activated protein C ratio in women with pre-eclampsia compared to controls. Many other studies have demonstrated the association between APC resistance and pre-eclampsia [27] [28] [29] [32] [40].

Some other studies, however, failed to demonstrate any association between activated protein C resistance and pre-eclampsia [33] [34] [35]. A recent study investigating the association of hereditary and acquired thrombophilia risk factors in the development of pregnancy complications in Croatia women assessed 101 women with pre-eclampsia and 102 healthy pregnant women and demonstrated only 1% association of Activated protein C resistance and pre-eclampsia [41]. Although it concluded that other inherited and acquired thrombophilic risk factors were found to be up to 10 times more common in the study group than in the control group. This study assessed a similar number of study participants and was able to establish an association between APC resistance and pre-eclampsia.

Deveer *et al.* also failed to demonstrate any association between factor V Leiden mutation and pre-eclampsia among 50 women with severe pre-eclampsia and 50 healthy pregnant women [34]. These studies are mainly in white populations and therefore variations in the reports from these studies may be attributed to racial differences which play an important role in the examinations of such correlation among different nations.

Rees *et al.* in 1995 assessed genetic data from 1690 unrelated individuals from 24 different populations for the presence of factor V Leiden as an important risk factor in venous thromboembolism and shows significant differences among different populations. Highest being Greek with prevalence of 7%, 4.4% in Europeans and 0.6% in Asia Minor. There was no factor V Leiden mutation found in Africa, Southeast Asia, Australasia, and the Americas. They confirmed a higher prevalence of the mutation among Europeans compared to individuals from other parts of the world [42].

However, a survey of a black population in South Africa studied similar numbers of patients to our study failed to demonstrate any association between factor V leiden and pre-eclampsia [36].

It is worthy of note that 4% of the normotensive pregnant controls had activated protein C resistance compared to controls. Our findings in this study are higher than 2% reported in the general population from a study in Lagos Nigeria [26]. A study from Enugu in South east Nigeria also demonstrated an increased incidence of activated protein C resistance among normal pregnant women compared to non-pregnant controls [43]. The increase incidence of APC-R may be attributed to increase in oestrogen levels, increase plasma volume; increased levels of some procoagulants e.g. factor VIII, decrease levels of some of the natural anticoagulants and reduced fibrinolysis [43].

Even though most studies done previously did not compare the degree of APC-resistance between patients with mild and severe pre-eclampsia, this study evaluated the difference between these two groups with respect to the values of APC ratio and the overall incidence of APC resistance. There was a significantly lower APC ratio in patients with severe pre-eclampsia compared with those with a mild form of the disease, and an overall higher prevalence of APC resistance in those with severe pre-eclampsia compared with mild pre-eclampsia. This finding suggests that worsening haemostatic process such as enhanced activation of the coagulation cascade and possibly impaired fibrinolysis associated with APC resistance may be implicated with worsening process of preeclampsia. This study is similar to an Iranian study which also assessed association between APC-ratio and severity of pre-eclampsia. The study, however, failed to demonstrate any association between them [30].

Recent studies shows that the combination of low dose aspirin and low molecular weight heparin if started before 12 weeks of gestation may be beneficial in women with APC resistance or other forms of thrombophilia who have previous history of pre-eclampsia especially those who had a severe form or early onset of the disease [44] [45].

APC ratio levels were also found to have a negative and significant correlation with the degree of proteinuria and mean arterial blood pressure, showing that APC ratio decreased with increasing severity of pre-eclampsia. This finding suggests that APC ratio may be used as a marker of severity in patients with pre-eclampsia and guide clinicians on appropriate decision making.

This study is limited by the non-inclusion of genetic studies making it impossible to determine if activated protein C resistance is due to hereditary or an acquired cause.

5. Conclusions

It can be concluded from this study that APC resistance is significantly more frequent in women with pre-eclampsia compared to normotensive pregnant women. APC-ratio is much lower in those with severe pre-eclampsia compared with those with mild disease and may therefore be used as a marker of severity in the disease.

The association of APC resistance with pre-eclampsia, especially with severe form of the disease suggests that at risk women should be enrolled early and screened for APC resistance before 12 weeks of pregnancy in view of possible therapeutic interventions. Such women should be followed up throughout pregnancy and puerperium.

It is, however, impossible from this study to determine whether this APC resistance is due to factor V Leiden or an acquired form of APC resistance. Further studies, including genetics as well as how environmental, lifestyle and socioeconomic factors might interact with genetic predisposition to affect the risk and severity of preeclampsia may be useful.

Conflicts of Interest

The authors declare no conflicts of interest.

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