

Associations between Preeclampsia and protein C levels among Sudanese pregnant women

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Abstract

Background:

Preeclampsia is considered to be the most prevalent hypertensive disorder of pregnancy, affecting 2–8% of all pregnancies, (1) Preeclampsia is best defined as an increase in blood pressure to 140/90 mm Hg or a 30/15-mm Hg increase over baseline after 20 weeks of gestation (2) According to the previous studies, preeclampsia is associated with decreased levels of coagulation inhibitor ,but protein C and protein S levels has not yet been fully clarified.(1).

Objective:

To determine the levels of protein C inhibitors in women with preeclampsia.

To determine whether thrombophilia increases the risk of preeclampsia.

Materials and Methods:

A case-control study was conducted at Omdurman Military Hospital - Khartoum State from 2016 to 2021 . Hundred pregnant women with preeclampsia (cases) in the 3rd trimester have been compared to 50 healthy normotensive pregnant women (control). Protein C level was determined using a sandwich ELISA.

Results:

No association was found in the level of protein C between women with preeclampsia and

normal pregnant women. The mean protein C level was $86.6 \pm \text{sd}$ and $86.4 \pm \text{sd}$ in the cases and the control group respectively. No significant differences were found between the two groups ($P=0.95$).

Conclusion:

There were no significant differences in protein C levels between women with preeclampsia and healthy pregnant women.

Keywords: Hypertension, normotensive, Pre-eclampsia, ProteinC, Proteinuria, Thrombophilia

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Introduction

Preeclampsia is a pregnancy-specific multi-system disorder that affects 3–5% of pregnant women worldwide and is one of the most frequently encountered medical complications of pregnancy(3). Preeclampsia is a severe pregnancy-related disorder associated with multiple maternal and fetal adverse outcomes (4) According to the World Health Organization (WHO), 800 pregnant women die every day of potentially preventable causes. Among these maternal deaths, 99% occur in developing countries with an incidence of approximately 240 deaths per 100,000 births (5)Preeclampsia presents with the onset of hypertension (arterial pressure exceeding 140/90 mmHg on at least 2 occasions, > 4 hours apart) in a previously normotensive woman. (6) accompanied by significant proteinuria (at least 30 mg/dl on a random urine sample or 300 mg in 24 hours) (7). However, a significant proportion of women develop systemic manifestations of preeclampsia—such as low platelets or elevated liver enzymes. In severe cases before the hallmark of proteinuria is detectable, the condition had been associated with seizures called eclampsia, liver and kidney damage, clotting abnormalities, and fetal growth restriction. These symptoms result in delayed diagnoses. (8) Despite decades of research, preeclampsia remains a complex medical disorder to fully understand. Indeed,

preeclampsia is a multisystem syndrome involving many genetic and environmental factors in its pathogenesis and pathophysiology. (9)

Many clinical risk factors for PE are well-established, including obesity, dyslipidemia, multifetal gestation, use of assisted reproductive technology, previous PE, and family history of PE or cardiovascular disease, Co-existing maternal medical conditions , like diabetes, chronic hypertension, renal disease, antiphospholipid antibody syndrome, increase PE risk (10)

The link between inherited thrombophilia and preeclampsia continues to remain disputed; data from some prospective cohort studies indicate that major thrombophilic factors are not associated with preeclampsia and screening is not useful for predicting the high risk of developing the disease but other studies suggest the opposite(11) that is Inherited thrombophilia is associated with an increased risk of thromboembolic complications. Classically it consists of Protein C and Protein S deficiency, activated Protein C resistance, and Antithrombin III deficiency. (12). In the last few years, the role of several markers has been tested to elucidate the pathophysiology of preeclampsia; numerous biochemical markers have been identified, including plasminogen activator inhibitor, placental growth factor, C-reactive protein, serum uric acid, inherited thrombophilia factor V Leiden mutation, protein C or S deficiency, antithrombin III deficiency (9) Protein C is a vitamin K–dependent serine protease zymogen in plasma which upon activation by thrombin in complex with thrombomodulin (TM) (13)Protein C activator acts as an anticoagulant by inactivating factors Va and VIIIa. Protein C active also exerts profibrinolytic properties by inactivating plasminogen activator inhibitor (14). On the contrary, there are no major changes in the levels of protein C in a normal pregnancy or the postpartum period., various studies suggest that preeclampsia is associated with decreased levels of protein C but not with further decrease in protein S level (15).The aim of the present study was, therefore, to determine whether there is an association between deficiency of protein C and preeclampsia among Sudanese women. This will help to establish whether there is a need for routine assay of protein C among pregnant women who are at a risk of preeclampsia.

Materials and Methods:

This is a hospital based case-control study .It was conducted in Omdurman Military Hospital- Khartoum State, between December 2016 and September 2021. The local ethical

committee approved the study protocol, and informed consent was obtained from the studied patients. The study included 100 preeclamptic women (age range of preeclamptic women was 17-40) in the 3rd trimester. The inclusion criteria of the study group were women with preeclampsia, and had blood pressure $>140/90$ mm Hg and proteinuria (Severe preeclampsia is characterized by blood pressure $> 160 / 110$ mmHg and protein urea more than 5 g / 24 hours) as a case. Exclusion criteria were congenital fetal anomalies, diabetes, and impaired renal function, in women with chronic hypertension or previous history of hypertension.

The control group was comprised of 50 Sudanese women with uncomplicated pregnancies. Fifty healthy women aged 17-40 with uncomplicated pregnancies were enrolled in the study as a control group. They had been subjected to clinical, biochemical, and ultrasound tests.

A written informed consent was taken from all the participants. 2 mL of the blood sample were taken from each participant in a vacuum tube containing sodium citrate (0.3ml of 3.2% sodium citrate) in a 9:1 volume ratio. All tubes were mixed by inverting the tubes 3-4 times immediately after the blood is drawn. Protein C assay was performed within 4 hours of sample collection, if there was any delay in performing the test then the platelet poor plasma (PPP) was frozen at -20°C for 2 weeks or at -70°C for 6 months. PPP was prepared by double centrifugation at 1500 g for 15 minutes with supernatant separated while care must be taken not to include the buffy coat. All cases were identified by numbers. Protein C levels were determined using a sandwich ELISA. The data in Microsoft Excel was exported to Statistical Package for Social Science (SPSS) version 22.01 ,which was used for data entry and analysis . The significance of difference in Cases and control was determined based on the calculation of p value. P-value less than 0.05 was considered significant.

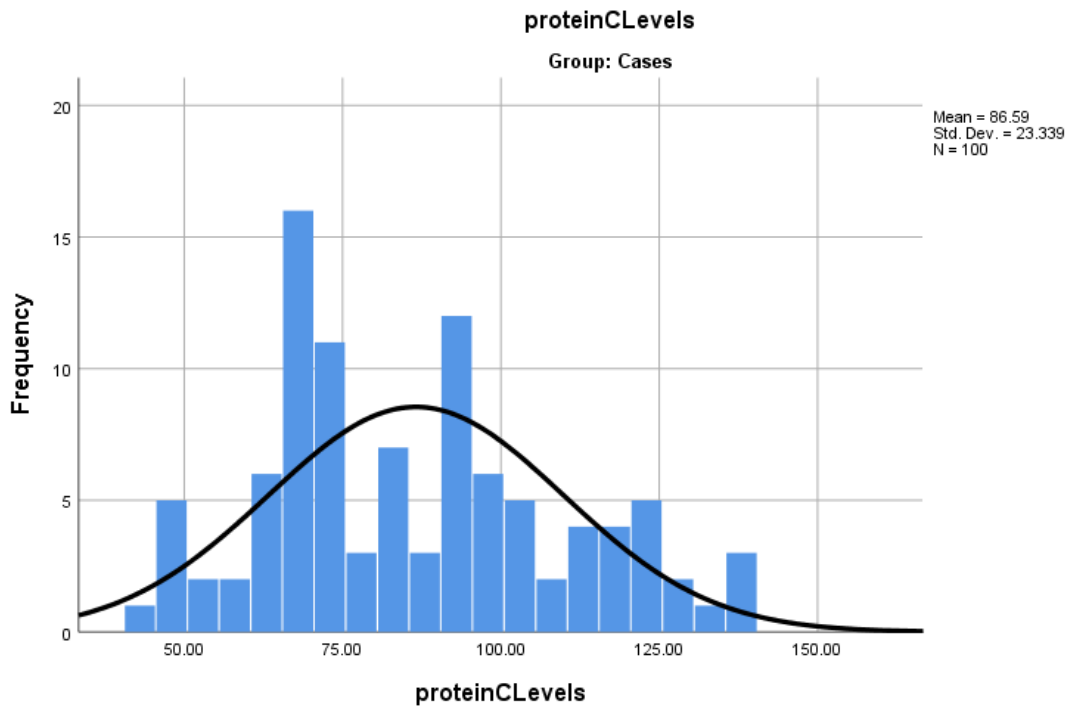
Results

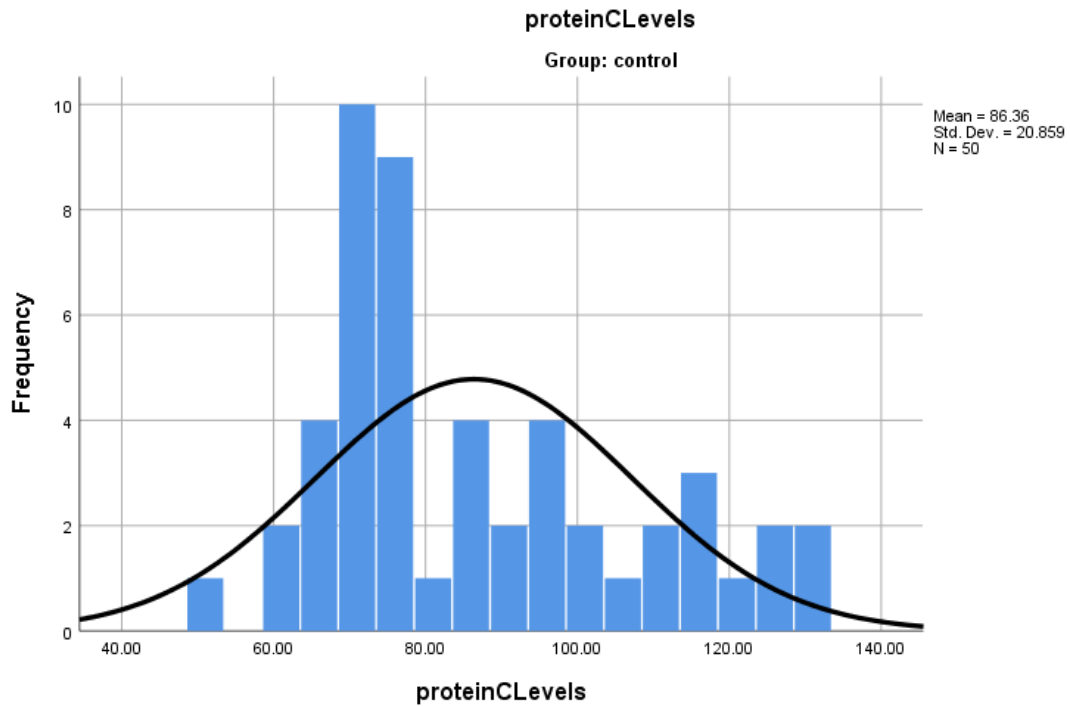
In total 150 pregnant women were recruited to the study , comprising 100 women with preeclampsia and 50 normotensive pregnant women (control group).The mean in cases was 86.6 while mean in control group was 86.4 and p value is 0.95 There are no significant

differences in the mean , medium levels of protein C between the preeclampsytic groups and the control (table 1).

Table 1: Frequency of protein C in case and control

Group	N	Minimum	Maximum	Mean	Std. Deviation	
Cases	proteinCLevels	100	43.00	140.00	86.5	23.33900
control	proteinCLevels	50	51.00	133.00	86.3	20.85886





Bivariate analysis:

Logistic regression:

Significance (p value: 0.95)

Odds ratio: 1

		B	S.E.	Wald	sdf	Sig.
Step 1 ^a	proteinCLevels	.000	.008	.004	1	.953
	Constant	.653	.691	.894	1	.344

Discussion

Proteins C and S are two vitamin K-dependent plasma proteins and are part of the natural anticoagulant system. Many pregnant women deficient in proteins C and S have been described and have an associated thrombotic tendency, but not all of them have experienced thrombotic complications (11). Although the level of protein S is thought to decrease in normal pregnancy, those of protein C and other natural anticoagulants like antithrombin III remain normal. Generally, a healthy pregnancy is regarded as a prothrombotic state. In our study, there was no statistically significant difference in protein C levels between preeclamptic women and controls and this study raises doubt about suspected pathophysiological mechanisms of preeclampsia in light of these insights. The data provided by Mirna Vukovic *et al.* were consistent with our results the authors reported There were no significant differences in protein C levels between women with preeclampsia and healthy pregnant women; however, six months after delivery protein S levels were significantly lower in women with preeclampsia as compared to healthy peers, whereas protein C levels did not differ significantly (15). In addition, the study of Giorgio Mello *et al* shows that the prevalence of each thrombophilia factor tested, for inherited deficiency of protein S, protein C, or antithrombin III, was the same in the test as in the control (16). The lack of association is likely attributable to the multifactorial nature of adverse obstetric outcomes, involving the interaction of epidemiological, clinical, and genetic risk factors(17). By contrast, Other researchers have shown a decrease in the concentration of natural coagulation factors in the development of large obstetric syndromes (preeclampsia, recurrent pregnancy loss) (18) Alfirevic *et al.* Found that women with pre-eclampsia are more likely to have protein C deficiency than normal pregnant women (19). Similarly f, Cengiz Demir *et al* found that protein C value of the preeclamptic pregnant women was lower than that of the control groups(20). In the present study this might be the result of racial differences because all individuals in the present study were black women who are known to have a high incidence of preeclampsia and low incidence of thrombophilia, unlike white women, who have a high incidence of thrombophilia. Another study emphasized that the decrease in PC levels might be related to increased consumption and the PC activity of preeclamptic pregnant women was lower than that of healthy pregnant and non-pregnant women .

Conclusion

The present study found that the mean level of protein C did not differ significantly between women with preeclampsia and normotensive women, as a result, does not support a role of thrombophilia in the pathogenesis of preeclampsia in Sudanese environment.

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