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Original Research Article

Evaluation of Protein C, Protein S and Antithrombin in Patients with Preeclampsia

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Abstract: The present study aims to measure protein C (PrC), free protein S (fPrS)and antithrombin (AT)in patients with preeclampsia (PE) and compare them with pregnant and non-pregnant controls (regarding PrC and fPr S)and to study the association between some haematological parameters with the level of natural anticoagulant in patients with preeclampsia . The case control study was done for fifty patients with preeclampsia, fifty for each healthy age matched pregnant and non-pregnant controls. Patients were diagnosed according to the diagnostic criteria of PEand were admitted to Al-Batool, Al-Khansaa and Al-Salaam Teaching Hospitals in Mosul between December 2012 and May 2013.Comparison between patients and pregnant controls was done in the natural anticoaulants: PrC level, fPr S level and AT level. PrC, fPr S level were done in non-pregnant controls as well for more confirmation. Other haematological parameters including platelet count (PLT), prothrombine time (PT) , activated partial thromboplastine time (APTT), fibrinogn level (FBG) and (D-dimer) where assessed in these patients to uncover any relative association with these natural anticoagulants level as well ,overall impact on the severity of the disease. A larger proportion of studied patients 70% were with severe PE, while 30% of them were with mild PE. PrC level was recognized to show significant decrease in patients with PE when compared to both pregnant and non-pregnant women. Free PrS level was significantly lower in patients with PE and control pregnant women when compared to non-pregnant controls ,yet, no significant difference was existed between patients and pregnant control AT was significantly lower in patients with PE as compared to the control pregnant group .Low AT was particularly in patients with severe PE and those with low PLT count and this was the only deduced association between the evaluated natural anticoagulants and the other haematological parameters in the study . Severe PE patients were recognized with a more significant reduced AT , FBG , and PLT as well more frequent shortened APTT and positive D-Dimer as compared to either mild and/ healthy pregnant groups .1. Plasma PrC level ,plasma fPr S level ,serum AT and plasma FBG level were decreased in PE patients and were significantly lower when compared to the control pregnant women apart from fPrS level which had no significant difference between both groups. 2. AT level show a significant association with PLT count . 3.Beside the known low platelet sign of sever PE, any of the following parameters (Low AT level , low FBG level , positive D-dimer , shortened APTT) can be considered as an estimating factor of the severity of PE.
Keywords: preeclampsia (PE), protein C (PrC), free protein S (fPrS)and antithrombin (AT)

INTRODUCTION

Preeclampsia is a multiorgan disease process of unknown aetiology [1], which is specific to pregnancy characterized by the development of hypertension and proteinuria after 20 weeks of gestation [2-5].

One of the most frequently proposed mechanisms for its development is uteroplacental thrombosis. Small placental thrombi are frequently observed in women with PE, suggesting that, in addition to the thrombotic nature of the placental vasculature, predisposing factors to thrombosis may cause or contribute to the development of this condition. This causes placental insufficiency with secondary placental damage in the form of fibrin deposition and thrombus formation. One of those predisposing factors for thrombosis is thrombophilia; a relationship between

hereditary thrombophilia, with preeclampsia development has been indicated [6].

Beside that preeclampsia by itself is a highly procoagulant state with risk of thromosis [7], the coagulation cascade is generally activated [8]. With platelet activation and consumption, promoting of thrombin formation and of fibrin formation [7]. Preeclampsia compared to normal pregnancy is also associated with significantly increased levels of thrombin antithrombin (TAT) complexes [9], while FBG is significantly reduced [6]. It has been recognized to show a decrease of the natural anticoagulants –PrC, Pr Sand AT [6.10]. Increased active protein Cresistance (APC-R) has been noticed in severe preeclamptic women [11].

That's why coagulation indexes may be of value in monitoring PE progress [12,13].

Protein C, Protein S and Antithrombin

Protein C circulates in plasma as a pro-enzyme. Its transformation into an active enzyme requires the presence of thrombin, calcium and phospholipids, thus the procoagulant signal generated by thrombin will be transformed into an anticoagulant response [14]. Its role in the anticoagulation system is to inactivate factor Va and Factor VIIIa. The first step, in this process, is the activation of thrombomodulin by thrombin. Subsequently, PrC combines with thrombomodulin in order to produce an activated PrC. Activated PrC, then combines with PrS on the surface of a platelet. Activated PrC can, then degrade factor Va and factor VIIIa [15]. Figure (I).

Protein S exists in both free (40%) and bound (60%) forms [14]. The complement4b binding protein (C4bBP) serves as a carrier protein for PrS [16]. Only the free form of PS participates in anticoagulation as a cofactor for APC while the complexed form loses its APC cofactor function [17].The free form of PrS enhances the binding of activated Protein C (APC) to phospholipids and, thus facilitates the cleavage of Factor Va and Factor VIIIa at arginine residues 306 and 336, respectively .Protein S can be a direct inhibitor, independently of PrC, and the interaction of PrS with the phospholipids surface is essential for the activated PrC independent activity of PrS [19]

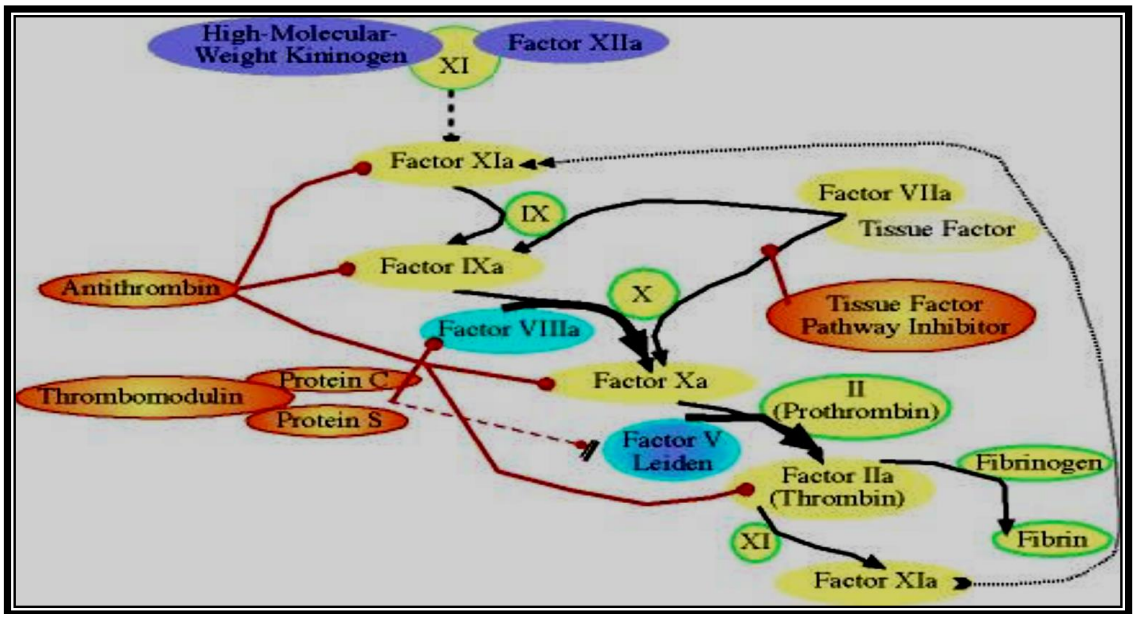

Fig-I : Blood Coagulation Pathway

Antithrombin (AT) is a potent inhibitor of the coagulation cascade. Itis a non- vitamin K-dependent protease that inhibits coagulation mainly by lysing thrombin and factor Xa. Antithrombin activity is markedly potentiated by heparin; potentiation of its activity is the principle mechanism by which both heparin and low molecular weight heparin act in anticoagulation [20].

Antithrombin inhibits FIXa, FXa, and thrombin, with its main targets being thrombin and FXa. It can also inhibit FXIa. Antithrombin inhibits its target by forming a 1:1 stoichiometric complex that

neutralizes the coagulation protease. The inhibitory reaction occurs in two steps: an initial weak association between the inhibitor and the protease, followed by the formation of a stable enzymatic complex that is cleared from the circulation .The complex formation between AT and its target proceeds at a very slow rate, while heparin accelerates the reaction approximately 1000 folds [21].

Aims of the Study

The present study attempts

- To measure PrC, PrS and AT in patients with
- PE and compare them with pregnant and non-pregnant controls (regarding PrC and fPr S).
- To evaluate and find out any association between some of the haematological parameters with the level of natural anticoagulants in patients with PE.

SUBJECTS AND METHODS

The case control study was conducted at the Departments of Gynecology and Obstetrics in Al-Batool Maternity Teaching Hospital, Al-Khansaa Teaching Hospital, Al-Salaam Teaching Hospital and at Hematology Lab at College of Medicine /University of Mosul. This study was approved by Ethic Committee .Informed consent was obtained from all participants. Blood was collected from:

Fifty pregnant women with PE who were diagnosed according to the diagnostic criteria (New onset of elevated blood pressure and proteinuria after 20 weeks of patients with essential hypertension, those with renal disease ,those with previous history or family history of thromboembolic phenomena and gestation) [3]. Exclusion was done for:
those who take drugs that interfere with coagulation such as heparin, salicylate, chlorpromazine,vitamin C, antihistamine and others.

- Fifty age matched healthy pregnant women.
- Fifty non -pregnant age matched healthy women.

Patients were categorized as mild or severe PE patients according to the criteria of severity of the disease.

A 5 ml of venous blood sample was collected from the pregnant women with PE and 5ml from each healthy pregnant women and from healthy non-pregnant women.1.8 ml venous blood was added into a clean plain capped disposable plastic tube containing 0.2 ml of 3.8 % (w\v) tri-sodium citrate after good mixing, the specimen was immediately or shortly after centrifuged at3000 r.p.m. for 15 minutes at room temperature to obtain platelet poor plasma. One ml of the obtained plasma was used for performing the following tests for patients:

Prothrombin time which was determined by using commercially available kit (BIO-TP \121004A\ France) depending on its reference value (11-15 sec). APTT was conducted by using commercially available kit (BIO-CK\031020A\France) depending on its reference value (30-40sec). For both PT and APTT, the test was conducted with control plasma obtained from healthy female donors. The end point clot detection was determined by the tilt tube method and the result was expressed in seconds. The Plasma FBG level determined, using commercially available kit (BIO-FIBRI \ 051218A\ France)that depends on the clot based method of Clauss for estimating the functional (clotable) FBG level. Reference value (2-4g/L).Plasma D-dimer reaction done for patients by using a commercially available kit (Atlas \12071522\UK) in which rapid latex agglutination slide test for the qualitative determination of the D-dimer reaction in plasma by agglutination of latex particle coated with anti-D-dimer monoclonal antibody.

All these tests were performed as early as possible on the freshly prepared plasma strictly within the time allowed by the manufacturer instructions of each kit.The remaining plasma was put in two plain tubes addressed with the name and the number of the participant and frozen in two separated sites at -20 ºC was expressed in seconds.

Antithrombin estimation is done by radial immune diffusion test using commercially available kit(IMMUNODIAGNOSTICKT\ 1485 A12 USA),Its reference value (2-35 mg/dL).Plasma PrC concentration is done by ELISA using commercially available kit (AESKULISA\Germany) which is a sandwich ELISA using microplates coated with a capture antibody specific for human PrC .Its reference value 70-140%.Plasma fPrS concentration evaluation by ELISA using commercially available kit (AESKULISA \Germany) which is a sandwich ELISA using microplates coated with a capture antibody specific for human PrS.Free Protein S. 50 -130%

RESULTS

The mean PrC level of PE patients was significantly less than that of the healthy pregnant controls and non-pregnant controls (P=0.038). The mean fPrS level of PE patients and of the healthy

pregnant controls was highly significantly lower than that of the non-pregnant controls (P =0.000).Table 1.

Table-1: Comparison of Mean Plasma PrC and fPrS between PE patients, Pregnant Controls and Non-pregnant Controls

Groups	PrC Mean± SD in(%)	P (0.038)	fPrS Mean± SD in(%)	P(0.000)
a/Preeclampsia Patients No.=50	90.80± 32.9 [b,c]		50.9 ± 11.6 [c]	
b /Pregnant Controls No.=50	101.20± 17.72		48.8 ± 12.6 [c] 0.000	
c /Non-pregnant Controls No.=50	102.78± 22.22		90.26 ± 22.3	

[b,c] Significant difference in comparison with pregnant and non-pregnant controls.
[C] Significant difference in comparison with non-pregnant controls.

The mean AT level in PE patients was highly significantly less than that of the healthy pregnant controls (P=0.000).Fibrinogen level as well, differed significantly in PE patients when compared to healthy pregnant controls (P =0.010) .Table (2).

Table-2: Comparison of Mean AT and Mean Fibr. Level between the PE Cases and Healthy Pregnant Controls

Groups	AT Mean± SD mg/dL	P =(0.000)	Fib . Mean ± SD g/L	P(0.010)
PE Patients No.=50	10.807 ± 5.732		2.533 ± 0.606	
Pregnant Control No.=50	16.452 ± 7.263		2.874 ± 0.684	

Among the studied anticoagulants only AT concentration was noticed to show significant variation between severe and mild PE .Table (3).

Table-3: Difference in the Mean of PrC, PrS and AT between Severe and Mild PE

Type of PE	PrC Mean± SD in(%)	P (0.752)	fPrS Mean± SD in (%)	P (0.718)	AT Mean± SD mg/dL	P(0.038)
Severe PE No.(35)	93.3 ± 30.2		51.3 ± 12.3		9.66 ± 5.41	
Mild PE No.(15)	90.2 ± 33.3		50.1 ± 10.3		13.48 ± 5.74	

No remarkable association between the studied parameters apart from that of the mean AT level and low platelet count, where patients with low PLT appeared a significant lower AT compared to patients with normal PLT count. Table (4).

Table-4: Difference in the Mean of AT Concentrations between Patients with Low ad Normal PLT

Parameter	Patients with low PLT No. (10) Low Platelet No. (10)	Patients with Norm. PLT No. (40) No. (40)	P-Value
Mean± SD of AT mg/dL	7.95 ± 4.11	11.52 ± 5.90	0.038

The proportion of positive D-dimer test and shortened APTT were higher in severe PE patients as compared to mild type. Table (5).

Table-5: Difference of Proportion of + D-dimer and Shortened APTT proportions between Mild and Severe PE

Groups	Proportion of + D-dimer	P(0.015)	Proportion of shortened APTT	P(0.032)
Sever PE	68.50%		48.57%	
Mild PE	33.40%		20%	

Low platelet and low FBG concentration means were distinguishing severe rather than mild PE when contrasted to pregnant controls. Table (6).

Table-6: Mean FBG. Level and PLT between Sever PE and Pregnant controls

Groups	Mean± SD of FBG. In g/L	P(0.00)	Mean± SD of PLT x10^9/L	P(0.007)
Severe PE	2.479 ± 0.625		183.6	
Pregnant control	2.874 ± 0.684		210.3	

DISCUSSION

In the current study a significant difference in PrC level was detected between PE patients and healthy pregnant controls and this was concordant with the findings of Demir C *et al*. and Onisai M *et al.* [22, 23]. On the other hand, no significant difference has been distinguished from the study of Osmanağaoğlu MA *et al*., the study of Heilmann L *et al*. and the study of Qattan MY between these two groups **[**24,25,16]. Since PE is a hypercoagulable state, the increased consumption of PrC might explain the low level of PrC in the current study, besides, PrC production may be decreased as a result of hepatic damage [16], and however, only two patients with an increased AST in their records had low level of PrC. Moreover, no significant difference in PrC level between the healthy pregnant controls and non-pregnant controls. This is an established fact, since in normal pregnancy PrC level does not show any changes [26].

When contrasting fPr S between PE patients and pregnant controls, no significant variation was considered in this study .This is consistent with the result of Heilmann L *et al*. [25] but not with those of Demir C *et al*. and Qattan M in which there was a significant decline in fPS level in PE patients compared to healthy pregnant controls [22, 16].

It is suggested that total and fPr S levels decrease gradually in healthy pregnant women during pregnancy, and this condition may be attributed to both increased PrC resistance and increased levels of coagulation factors [22]. In the current study, fPr S level in the preeclamptic patients and healthy pregnant controls significantly showed reduction in its level more than that of non-pregnant controls. This is an agreement with the studies of Demir C *et al*., Qattan MY, Yalinkya *et al*. and Sayin M *et al*. [22,16,27,28].

The AT level in the studied patients significantly dropped as compared to the healthy pregnant group. This is accordant with the results of studies of Heilmann L *et al*., Demir C et al and of Onisai M *et al*. [25,22,23].

The first two have revealed that AT level shows more reduction in severe PE compared to mild PE. Osmanağaoğlu MA *et al*. mentioned that AT level was only lower in severe PE compared to the pregnant controls [24]. In this study, the lower AT level was the more severe the disease and the lower platelet count. The decreased AT level can be explained by the fact that the prevailing excessive thrombin formation that occurs in PE is physiologically compensated by a rise in thrombin-antithrombin (TAT complex levels, and a decrease in antithrombin AT level) [29].

The possibility of hereditary deficiency of the natural anticoagulants (PrC, Pr S and AT) can be claimed for the decrease noticed in the current study, however, negative previous history of thromboembolic phenomena and negative family history of thromboembolic disease were insured to be negative from the selected patients . Post partum estimation of these natural anticoagulants is the cut off point in defining genetic or acquired cause of these deficiencies. Beside, the hereditary deficiency of PrC, PrS and AT is considered the less common among hereditary thrombophilia and if present, augmentation of the pathophysiological process of PE is aggravated rather than a real act in the pathogenesis of the disease [30,31].

The mean FBG level in PE patients was significantly more depleted in severe rather than mild PE when compared to the control pregnant group. The study of Qattan MY and the study of Awodu OA et al have observed that FBG level was increased in PE [16,32] ,while that of Ibrahim AM has come with a decreased FBG level in PE [33]. Osmanağaoğlu MA *et al*. stated that there was no significant difference in the FBG level in PE and healthy pregnant controls [24].

Decreased FBG is a possible hemostatic change that can occur especially in severe PE and this can be a part of a non-compensated DIC with hemodynamic stability [34].

Plasma D-dimer is a well established clinical laboratory marker of fibrin polymerization and breakdown in vivo [35]. In this study D-dimer was positive in 58% of the cases and its proportion was significantly higher in patients with the severe type than mild type of PE. These results are almost as those of Ibrahim AM study in which positive D-dimer have constituted about 51.6% of the patients [33]. Application of D-dimer estimation by ELISA can give more accurate estimation with high negative predictive value in the evaluation of the thrombotic state of the disease [36].

All PT tests were within normal range (results figures not stated here) alike the test results of Osmanağaoğlu MA *et al*. and Qattan MY study [24,16].

In the current study, a significant difference in the proportion of shortened APTT was also encountered between mild PE patients and severe PE patients as it was more shortened in severe type and this has been asserted by the study of Ibraheem AM [33].

Shortened APTT in pregnancy is mainly contributed by hormonally induced increase in factor VIII and is associated with excessive thrombin formation which is the ultimate result of exaggerated hyperocoagulability that is present in PE [37, 38].

Prolonged PT and APTT are features of acute rather than chronic DIC, as both depend on the ultimate conversion of FBG to fibrin, they are prolonged when FBG level is equal or lower than 1g/L [33]. In the studied patients, the minimum plasma FBG level was 1.48 g/L and that is why PT and APTT prolongation were not encountered in the majority of them.

Mean platelet count of severe PE was significantly lower than that of the control pregnant women. This can be explained since, PE represent a hypercoagulable state with increased platelet activation and consumption [39]. Beside that thrombocytopenia is a known factor of severe PE [40]. Similar difference between mean platelet counts was also observed between patients with severe PE and control pregnant women in the study of Osmanağaoğlu MA *et al*. [24].

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