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Short Communication

Protein S and protein C in preeclamptic pregnant women

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Abstract

Background and purpose: *Deficits of protein C and protein S are associated with an increased incidence of thrombotic disorders. The aim of the present study was to determine the levels of the mentioned natural coagulation inhibitors in women with preeclampsia and in a 6-months follow-up period after delivery.*

Materials and methods: *This case-control clinical study included 55 pregnant women (cases) with preeclampsia and 50 healthy normotensive pregnant women (controls) in tertiary perinatal centre. Protein C levels were determined photometrically using a chromogen substrate, and protein S levels were determined using the clot method and optic detection.*

Results: *There were no significant differences in protein C and protein S 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.*

Conclusion: *Possible long-term cardiovascular morbidity should be assessed in preeclampsia women.*

INTRODUCTION

Deficits of protein C and protein S are associated with an increased incidence of thrombotic disorders (*1–3*). The levels of free and bound protein S decline in pregnancy; the level of functional protein S remains at 40-50% of normal until the first few days after delivery (*1*). On the contrary, there are no major changes in the levels of protein C in normal pregnancy or in the postpartum period. According to the previous studies, in comparison with normal pregnancy, preeclampsia is associated with decreased levels of protein C but not with further decrease in protein S level (*3*). Results of various studies suggest that the association of preeclampsia with protein C and protein S levels has not yet been fully clarified.

The aim of the present study was to determine the levels of the natural coagulation inhibitors protein C and protein S in preeclamptic pregnant women and in the postpartum 6 months follow-up.

MATERIAL AND METHODS

Patients

The study was approved by the Institutional Ethics Committee and conducted in accordance with the principles of the Helsinki Declara-

tion. This case-control clinical study included 55 pregnant women (cases) with preeclampsia and 50 healthy normotensive pregnant women (controls) in tertiary perinatal centre, Clinical Hospital Osijek. Prior to entering the study, all women were informed of the purpose, protocol, and objectives of the study. Pregnant women with preeclampsia and healthy pregnant women (controls) were included in this study on their regular third trimester prenatal visit (32 weeks). Healthy pregnant women are free of any comorbidities and risk factors for pathological hypercoagulable conditions.

Methods

Cases had no prior arterial hypertension or renal disease in their medical history and were diagnosed with mild preeclampsia in index pregnancy (blood pressure measurements on at least two occasions at minimum 4h interval ≥ 140/90-160/110 mm Hg and with positive proteinuria after 20th week of gestation). Protein C levels were determined photometrically using a chromogen substrate, whereby the rise in absorbance to 405 nm is measured by a kinetic assay on a BCT device (Dade Behring Marburg GmbH®, Germany) using a test kit code OUVV17 from the same manufacturer. Protein S levels were determined using the clot method and optic detection on a BCT device (Dade Behring Marburg GmbH®, Germany) using a test kit code OPAP from the same manufacturer.

Statistical analysis

Continuous variables were summarized as mean (standard deviation) and categorical variables as absolute (relative) frequencies. Shapiro-Wilk test was used to test distribution normality. T-test, Levene test, and χ^2-test were used for intergroup comparisons. All tests were two-sided and level of significance was set at $p<0.05$. Data were analysed using Microsoft Excel.

RESULTS

Demographic data are presented in Table 1. The groups did differ in age and parity; preeclamptic women had a significantly shorter gestational age and number of comorbidities ($p<0.001$, and $p<0.001$), respectively. In women with preeclampsia, the mean protein C level was 1.313±0.353 IU/L. In control group, the mean protein C level was 1.205±0.217 IU/L ($p=0.058$). In women with preeclampsia, the mean protein S level was 0.593±0.139. In control group, the mean protein S level was 0.596±0.117 IU/L ($p=0.909$). In women with the preeclampsia, six months after delivery, the mean protein C levels were 1.290±0.262 IU/L; compared to baseline, the difference was not statistically significant ($p=0.524$). The mean protein S levels were 0.784±0.157 IU/L; compared to baseline, the difference was statistically significant ($p<0.001$).

DISCUSSION

Hypothesis that reduced protein C and protein S levels cause a general procoagulant state with placental vascular involvement, thus enabling the occurrence of microthrombi, increased vascular resistance, and sustain the pathologic mechanisms of preeclampsia can be presumed from previous studies. Authors of these studies conclude that in the presence of preeclampsia, the levels of protein C and protein S are lower than the respective values in normal pregnancy or non-pregnancy (*4–6*). Pregnancy-dependent hemodilution is proposed as a basic pathophysiological mechanism of preeclampsia to be directly related to the observed reduction of levels of coagulation inhibitors (*7, 8*). Considering the natural coagulation inhibitors and knowing that pregnancy itself is a prothrombotic condition, a decline would be expected in the levels of both parameters tested (protein C and protein S in both groups), with a greater decrease in preeclamptic women (*4–6*, *9–11*). In our study, there was no statistically significant difference in protein C and protein S levels between preeclamptic women and controls and this study raises doubt in suspected pathophysiological mechanisms of preeclampsia and in light of these insights, we hold that further research is warranted.

Other researchers have shown a decrease in the concentration of natural coagulation factors in the development of large obstetric syndromes (preeclampsia, recurrent pregnancy loss) associated with thrombophilia, and thus low values of protein S as an isolated risk factor (*13, 14*), but some previous studies showed no correlation between these factors and protein S levels, which interprets the heterogeneity of the study and requires further randomized evaluation (*15, 16*). It is important to point out that we only analysed the levels of coagulation factors from the mother's circulation, not in fetoplacental (umbilical) circulation. Additionally, our study had a relatively short follow-up

Table 1. *Summary of patient data*

	Preeclamptic women (*N*=55)	Healthy pregnant women (*N*=50)	P
Age (years, mean)	29.97	27.88	<0.001*
Gestational age (weeks, mean)	35	39	<0.001*
Parity *(n)*			<0.001**
0	5	0	
1	35	32	
2	11	13	
3	2	3	
4	1	2	
5	1	0	
Comorbidity *(n)*			<0.001**
Gestational diabetes	3	0	

*t-test; **χ^2-test

period and a relatively small sample size, but statistically relevant and adequate for conclusions.

We found no statistically significant differences in protein C and protein S levels between pregnant women with preeclampsia and healthy pregnant women; however, protein S levels were significantly lower in preeclamptic women six months postpartum compared to baseline; protein C levels did not differ significantly. Studies are underway to assess the possible long-term cardiovascular morbidity associated with the significant decline in protein S level six months postpartum in preeclampsia women.

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