

# The Plasma Levels of Protein S and Protein C Activities among the Pregnant Women with and without Pre-eclampsia

Sanya Prabripataloong<sup>1</sup>, Somchai Insiripong<sup>2</sup>

Department of <sup>1</sup>Obstetrics and Gynecology, <sup>2</sup>Medicine, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, 30000 Thailand

Correspondence to: Sanya Prabripataloong, M.D.

Department of Obstetrics and Gynecology, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, 30000 Thailand

**Background and objective :** Protein S and protein C deficiencies are more common among Thais and protein S deficiency was found to be associated with one-fourth of cases of severe pre-eclampsia among westerners. This study aims to compare the levels of protein S and protein C activities between the pre-eclamptic and normal pregnancies

**Method:** The levels of protein S and protein C activities from the pre-eclamptic and from the age-, the gestational age-, and the parity-matched normal pregnancies as control were compared and analyzed.

**Results:** The levels of protein S activity from the pre-eclamptic group was  $27.4 \pm 30.0$  % which was not statistically different from  $17.8 \pm 21.0$  % of the control ( $p = 0.1002$ ). The deficiency of protein S was found in 17 of 41 pre-eclamptic patients (41.5%), comparable to 18 of 41 control (43.9%) ( $p = 0.823$ ). Protein C activity was similarly normal in both groups.

**Conclusion:** The levels of protein S activity from the pre-eclamptic and the normal pregnancies were similarly decreased whereas the protein C activity was equally normal in both groups.

**Keywords:** Protein S Activity, Protein C Activity, Pre-eclampsia

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## Introduction

Pre-eclampsia is one of the common complications of pregnancy and one of causes of maternal death. Its clinical manifestations consist of edema, high blood pressure of more than 140/90 mmHg, and albuminuria of more than 300 mg a day<sup>1</sup>. Although its pathogenetic mechanism is not clearly understood, it is found to be associated with various conditions such as: maternal age > 35 years, nulliparity, prepregnancy body mass index (BMI) > 30 kg/m<sup>2</sup>, multifetal pregnancy, history of preeclampsia in a previous pregnancy and chronic hypertension whereas the maternal age < 20 years and the

pregnancy BMI < 20 kg/m<sup>2</sup> are found to be the protective factors against pre-eclampsia in Thais<sup>2</sup>.

In Thailand, the prevalence of protein S deficiency is actually found to be 3.7 %<sup>3</sup> which is much higher than 0.03-0.13 % among Caucasians<sup>(4)</sup> and of the protein C deficiency is 0.27 %. In fact, the main clinical manifestations of protein S or protein C deficiency are deep venous thrombosis and pulmonary embolism<sup>5-7</sup> but protein S deficiency and activated protein C resistance are found in 24.7% and in 16 % of cases with severe pre-eclampsia respectively<sup>8</sup>. The large multicenter observational cohort study mentioned many thrombophilic factors in-



cluding factor V Leiden and factor II G20210A mutations, hyperhomocystinemia, lupus anticoagulant, and anticardiolipin antibodies are associated with a higher risk for the recurrence of preeclampsia (odds ratio, 2.5; 95% confidence interval, 1.2-5.1), compared to patients without thrombophilia while protein S, protein C and antithrombin deficiencies are found only in three cases, and there was no recurrence of pre-eclampsia but the numbers are too to be draw any conclusion<sup>9</sup>.

While the prevalence of pre-eclampsia is commonly found, 3.7-5.3%<sup>10</sup>, the association of protein S and protein C deficiencies and pre-eclampsia among Thais has so far never been mentioned.

This study was aimed to study and to compare the plasma levels of protein S and protein C activities between the pre-eclamptic group and the normal pregnancy group.

#### Patients and Methods

This cross-sectional study recruited the consecutive severe pre-eclamptic patients who fulfilled one of the following criteria, i.e., blood pressure 160/110 mmHg or more, proteinuria 2 gm/24 hours, serum creatinin 1.2 gm/dl, platelet below 100,000 mm<sup>3</sup>, increase lactate dehydrogenase (LDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), cerebral or visual disturbance, epigastric pain. The exclusion criteria were the pregnant women who had any chronic disease, prepregnancy body mass index more than 30 kg/m<sup>2</sup>, blurred consciousness, high blood pressure before the second half of pregnancy, impaired kidney or liver function or maternal age less than 15 years.

The controlled group were the pregnant women who were age-, gestational age- and the parity-matched.

The sample size was calculated to be at least 40/group, according to the figures of the previous studies, i.e., the prevalences of protein S were 3.7% in the population and 24.7% in the pre-eclamptic patients. The alpha error was 0.05 whereas the beta error was 0.2.

The blood samples were drawn and mixed promptly with sodium citrate and centrifuged for the collection of plasma. And the plasma would be frozen and sent to the laboratory service of Ramathibodi Hospital, Bangkok where the plasma level of protein S and protein C activities would be verified using ACL, 8,000 respectively.

The levels of protein S and protein C were expressed as the percentage of activity, and the student-T as well as chi-square tests between 2 unpaired populations was used to analyze the data. If the p-value was less than 0.05, it would be considered different with statistical significance.

This study was approved by the ethic committee of Maharat Nakhon Ratchasima Hospital.

#### Results

There were 41 participants from each group, the pre-eclamptic and the normal pregnant groups. The general characteristics from both groups were shown in the table 1.

**Table 1** The general characteristics from the pre-eclamptic and the normal pregnant groups (N=41)

	pre-eclamptic mean ± SD	Normal pregnant mean ± SD
Age (years)	25.8±7.5	25.9±8.8
Gestational age (weeks)	36.1±2.7	38.3±1.5
Gravida		
1	23	20
2	12	11
3	5	7
4	1	2
5	0	1
Parity		
0	26	22
1	11	11
2	4	7
3	0	1

The levels of protein S and protein C activities among the pre-eclamptic and normal pregnant groups were shown in the table 2 and the numbers of protein S deficiency in each group were shown in the Table 3

**Table 2** The levels of protein S and protein C activities among pre-eclamptic and normal pregnant groups with p-value by Student-T test

	Pre-eclamptic	normal pregnant	p-value
Protein S			
Means	27.4±30.0	17.8±21.0	0.1002
Median	18	5	
Protein C			
Means	78.1±33.3	84.5±33.1	0.3829
Median	69	75	

**Table 3** Numbers of protein S deficiency in pre-eclamptic and in normal pregnant groups. (N=41)

	Pre-eclamptic	normal pregnant
Protein S		
Absence	17 (41.5%)	18 (43.9%)
Presence	24 (58.5%)	23 (56.1%)
Total	41	41

Chi-square 0.498, p = 0.823

**Table 4** The level of protein S activities.

	pre-eclamptic n (%)	normal pregnant n (%)
Protein S		
Absent	17 (41.5)	18 (43.9)
Decreased	18 (43.9)	22 (53.7)
Normal	6 (14.6)	1 (2.4)

Chi-square = 4.00, degrees of freedom = 2, probability = 0.135

When the levels of protein S and protein C activities were classified into 3 classes according to the intervals: absent- the activity zero, decreased- the activity between 1- 60 %, for protein S and between 1-63 % for protein C and normal-the activity between 61-127 % for protein S and between 64-141 % for protein C, the numbers of each class from the pre-eclamptic and the normal pregnant groups were shown as in the Table 4-5

**Table 5** The level of protein C activities.

	pre-eclamptic n (%)	normal pregnant n (%)
Protein C		
Decreased	15 (36.6)	10 (24.4)
Normal	26 (63.4)	31 (75.6)

Chi-square = 1.44, degrees of freedom = 1, probability = 0.230

## Discussion

The numbers of the pregnant women with deficiency of protein S activity in the pre-eclamptic group are found to be 41.5% which are much higher than that of the general population of Thailand (3.7%) but not different from those of the normal pregnant group (43.9%). One of the proposed pathogenetic mechanisms is the placental vascular insufficiency which leads to the release of the mediators into the maternal circulation, leading to preeclampsia<sup>1</sup>. Although the placental insufficiency can be caused by the thrombosis of the placental vessels due to various hypercoagulable factors such as protein S, protein C, or antithrombin deficiency<sup>11</sup> but fails to show the association of protein S or protein C deficiency and the pre-eclampsia.

In one case-control study, the severe pre-eclampsia is not associated with protein S, protein C or antithrombin III deficiency<sup>12</sup>.

As the natural anticoagulant, its deficiency during preg-



nancy imposes the hypercoagulable state but not the preeclampsia on the pregnant women.

The findings of decreased level of protein S activity but normal level of protein C activity are similarly found in both pre-eclamptic and normal pregnant groups and they confirm the fact that the level of protein S activity is gradually decreased during the pregnant period, the degree of decrease is progressive according to more gestational age while the protein C is not affected through the pregnancy period<sup>13</sup>.

However the study of the level of protein S activity among the pregnant women with or without pre-eclampsia should be repeated after the postpartum period, particularly the ones whose protein S activity is deficient<sup>14</sup>.

In conclusion, the prevalence of deficiency of protein S activity is equally high in pregnancies both with and without preeclampsia but the protein C activity is not affected by pregnancy.

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