The relationship between pregnancy induced hypertension and congenital thrombophilia

S. Cansun Demir, MD, Cuneyt Evruke, MD, Tuncay Ozgunen, MD, Oktay Kadayifci, MD, Umit Altintas, MD, Sehim Kokangul, MD.

ABSTRACT

Objective: To investigate the relationship between some thrombophilic parameters and pregnancy induced hypertension (PIH).

Methods: The study took place at the Department of Obstetrics and Gynecology, Perinatology Unit, Faculty of Medicine, Cukurova University, Turkey, between January 2002 and December 2002. We evaluated 202 patients. Patients were divided into 2 groups: control group comprised 102 normotensive patients >20 weeks of pregnancy without any medical or pregnancy related pathologies and the study group comprised 100 patients over 20 weeks of pregnancy with PIH. These hypertensive patients were divided into 6 sub-groups as follows: eclampsia, severe preeclampsia, preeclampsia, chronic hypertension plus superimposed preeclampsia, eclampsia, and hemolysis elevated liver enzymes and thrombocytopenia (HELLP) syndrome.

Results: In all cases, complete blood count, antithrombin III, protein S levels, factor V Leiden mutation, prothrombin 20210 mutation, methylenetetrahydrofolate reductase (MTHFR) 677 mutation and homocysteine levels were studied. Statistical analysis of the data was carried out using SPSS version 11.0 program. In comparing the 2 groups we used Mann-Whitney U tests. In comparing the PIH subgroups we used Kruskal-Wallis tests. The levels of $p<0.05$ were accepted as statistically significant.

Conclusion: Antithrombin III deficiency, protein C deficiency, hyperhomocysteinanemia were found to be associated with PIH groups. But protein S deficiency, and homozygote factor V Leiden mutation, prothrombin 20210, MTHFR 677 mutation were not found to be related with PIH.

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Pregnancy induced hypertension (PIH) and the complications of hypertension are leading to maternal and perinatal mortality and morbidity. Pregnancy induced hypertension is a problem in 5-7% of the pregnant women who were healthy before the pregnancy, but its incidence is 20-40% among women with chronic renal or vascular disease. Pregnancy induced hypertension may lead to fetal intrauterine growth retardation, prematurity, stillbirth, placental abruption, and to maternal problems such as: cerebrovascular problems, blindness, pulmonary edema, heart failure, renal failure, and may even cause death.[1,2] There are many theories on the etiology of preeclampsia, but still the real reason is not clear. One of the newest theories is the relationship of thrombophilic disease and some problems in pregnancy such as preeclampsia, intrauterine fetal retardation, and fetal loss. Thrombophilia is a word used to define a situation with a tendency to thrombosis. In some studies, it was found that coagulation abnormalities (which are thrombophilias) are related with PIH.[3-8] In the literature there are also

From the Department of Obstetrics and Gynecology (Demir, Evruke, Ozgünen, Kadayifci, Altintas), Faculty of Medicine, Cukurova University Balcali, Adana, *Turkey,* Department of Obstetrics and Gynecology (Kokangul), Bethenien Krankenhaus Iserlohn, *Germany.*

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Address correspondence and reprint request to: Dr. Cansun Demir, Department of Obstetrics and Gynecology, Faculty of Medicine, Cukurova University Balcali, Adana, *Turkey.* Tel. +90 (322) 3387228. Fax. +90 (322) 3387228. E-mail: scdemir@mail.cu.edu.tr

studies which report that the presence of prothrombic factors in healthy nulliparous women does not compromise blood flow in the feto-maternal unit, nor it is associated with preeclampsia, intrauterine growth restriction, or small for gestational age.[9] The early diagnosis of preeclampsia is a major problem not only for obstetrical reasons, but also as a public health problem especially in developing countries such as Turkey. The aim of this study is to investigate the relationship between PIH and some thrombophilic factors which are detected in the blood. If we find a relationship between thrombophilia and PIH, then a test of thrombophilia may be used instead of, for example; uterine artery Doppler for detection of preeclampsia before it occurs.

Methods. The study was conducted in the Department of Obstetrics and Gynecology, Perinatology Unit, Faculty of Medicine, Cukurova University, Turkey, between January 2002 and December 2002. This study was approved by the Ethical Committee of Cukurova University and all participants had given written informed consent to participate in the study. Two hundred and two women were evaluated in this study. The patients were divided into 2 groups: First group was the study group (PIH group) comprised 100 pregnant women who were hospitalized for PIH and had >20 weeks pregnancy. These PIH patients were divided into 6 subgroups such as 1. Eclampsia (who had seizure or coma during pregnancy). 2. Severe preeclampsia (who had blood pressure >160/110 mm Hg, proteinuria >5 gr/day, generalized edema, cyanosis, oliguria and prodromal signs as headache or scotoma and so forth). 3. Preeclampsia (edema, proteinuria >0.3 gr/day, hypertension blood pressure >140/90 mm Hg). 4. Chronic hypertension superimposed preeclampsia, (preeclampsia criteria's occurred in a chronic hypertensive patient). 5. Hemolysis elevated liver enzymes and thrombocytopenia (HELLP) syndrome. 6. Eclampsia with HELLP syndrome (A patient who had eclampsia and HELLP syndrome together). Second group was the control group comprise 102 normotensive patients who were followed up in the outpatient clinic, had pregnancy of >20 weeks, with normal pregnancy and without any pathologies.

We obtained the peripheric venous blood in an appropriate conditions using Vacutainer (a vacuum system). For protein C, protein S and Antithrombin III levels, we took 4.5 cc of blood from a tube with 0.5 cc of sodium citrate, and was studied in the hematology laboratory using chromogenic method. Factor V Leiden mutation, prothrombin 20210 mutation, and MTHFR 677 mutation were studied by means of ethylenediaminetetraacetic acid (EDTA) and was stored at $+4^0$C. We analyzed the DNA with the used of polymerase chain reaction method. Homocysteine was studied with 5 cc blood, which was taken into empty tubes. The results of antithrombin III, protein C and protein S results were given as %, homocysteine was given as mmol/L and Factor V Leiden, prothrombin 20210 and MTHFR 677 mutation were given as homozygote mutant, heterozygote mutants or normal (without mutation).

All analyses were conducted using SPSS statistical software Version 11.0. We used Mann-Whitney U test in comparing the 2 groups. In comparing the 6 subgroups of the study group, we used the nonparametric variance analysis method and Kruskal-Wallis method. A P value of <0.05 was considered statistically significant.

Results. This study comprised 102 control and 100 study (PIH) patients. The diagnosis of the 2 groups are shown in **Table 1**. The age difference of the 2 groups was not statistically significant (p=0.579). The chronic hypertension super-imposed preeclampsia group (PIH group) the mean age was higher than the other groups. The mean parity of PIH was 2 but in the chronic hypertension superimposed pregnancy group the mean parity was 6. The mean values and the comparison of the control group and the PIH (study) subgroups are shown in **Table 2**. The difference of all the values between the subgroups were statistically significant ($p<0.05$). Antithrombin III levels of the control group are statistically significantly higher than the PIH group (p=0.000). The levels of protein C was statistically significantly lower in the study groups than the control group (p=0.000). The difference was most

Table 1 - Diagnosis seen in 2 groups (control and pregnancy induced hypertension groups).

Diagnosis	Number of patients (%)	
Control	102	(50.5)
Eclampsia	14	(7)
Severe preeclampsia	20	(10)
Preeclampsia	36	(17.5)
Chronic hypertension and super-imposed preeclampsia	10	(5)
HELLP syndrome	10	(5)
Eclampsia and HELLP syndrome	10	(5)
Total	**202**	**(100)**

HELLP - Hemolysis elevated liver enzymes and thrombocytopenia

Table 2 - The mean antithrombin III, protein C , protein S, and homocysteine results of the control and PIH subgroup patients .

Thrombophilia	Control	Severe preeclampsia	Eclampsia	Preeclampsia	Chronic hypertension and superimposed preeclampsia	HELLP syndrome	Eclampsia and HELLP syndrome	*P*-value (subgroups)
Antithrombin III	106.10	94.77	83.71	88.33	84	94.80	81.60	0.00
Protein C	106.42	96.2222	79.2857	89.4444	89	90	99.2000	0.00
Protein S	40.6600	45.2222	41.8571	43.0556	70	44.4000	39	0.025
Homocysteine	7.6206	13.1067	20.0443	9.7494	7.3700	8.5320	15.4880	0.002

PIH - pregnancy induced hypertension, HELLP - Hemolysis elevated liver enzymes and thrombocytopenia syndrome

Table 3 - The mean antithrombin III, protein C , protein S, and homocysteine results of the control and PIH subgroup patients .

Mutation	Control	Eclampsia	Severe preeclampsia	Preeclampsia	Chronic hypertension + superimposed preeclampsia	HELLP syndrome	Eclampsia + HELLP syndrome	Total	*P*-value
Factor V Leiden	5	4	2	4	-	2	-	17	0.115
Prothrombin 20210	7	2	3	-	-	-	-	12	0.275
MTHFR Heterozygote	47	10	15	14	4	6	4	100	0.041
MTHFR Homozygote	12	2	2	6	4	-	-	26	0.041

PIH - pregnancy induced hypertension, MTHFR - methylenetetrahydrofolate reductase
HELLP - Hemolysis elevated liver enzymes and thrombocytopenia syndrome

significant in the eclampsia group. Protein S levels were statistically significantly higher in the chronic hypertension and superimposed preeclampsia group (PIH group) (p=0.000). Thus, the overall evaluation of the subgroups revealed no statistically significance. There was no significant difference among the 2 groups (p=0.115). When homocysteine levels were studied, it was found that homocysteine levels were statistically significantly different between the PIH subgroups (p=0.002). Homocysteine levels of the PIH group were statistically significantly higher than the control group (p=0.003). The results of the mutations of Factor V Leiden, prothrombin 20210, MTHFR of the control, and PIH subgroup patients is shown in **Table 3**. According to Factor V Leiden Mutation and prothrombin 20210 mutation there were no significant difference was found between the control and the PIH subgroups, but there was a statistically significantly difference regarding MTHFR mutation (homozygote and heterozygote). The MTHFR 677 homozygote mutations was higher in the chronic hypertension superimposed preeclampsia subgroup and the heterozygote mutation was higher in the eclampsia, severe preeclampsia, HELLP syndrome groups. The comparison of the MTHFR 677, prothrombin 20210 and Factor V Leiden mutation results for the control and the PIH groups were shown in **Table 4**.

Discussion. The age of the patients was similar in both PIH group and the control groups. The parity of the patients were one in HELLP syndrome, 2 in control, eclampsia, severe preeclampsia, preeclampsia group and it was 3 in the eclampsia with HELLP syndrome group and 6 in the chronic hypertension superimposed preeclampsia group. In the literature, chronic hypertension superimposed preeclampsia was a disease of multigravida patients as in our study, but eclampsia and preeclampsia was a disease of the primigravida and the young patients in the literature, which was different from our results.[2,10] Antithrombin III results were significantly lower in the PIH groups, especially in the eclampsia, chronic hypertension superimposed preeclampsia and eclampsia plus HELLP syndrome groups than the control group. In the literature, many studies reported similar results that PIH patients had lower antithrombin III levels than the normotensive cases.[11-13] In Heilmann et al[14] study, it was found that there was significant difference between preeclampsia and control group,

Table 4 - Number of patients in the control and the PIH groups for the MTHFR 677, prothrombin 20210 and Factor V Leiden mutation.

Mutation	MTHFR 677 mutation		Prothrombin 20210 mutation		Factor V Leiden mutation	
	Control	PIH	Control	PIH	Control	PIH
Healthy	43	33	95	95	97	88
Heterozygote	47	53	7	5	5	12
Homozygote	12	14	-	-	-	-
Total	**102**	**100**	**102**	**100**	**102**	**100**
P-value	0.189		0.0531		0.084	

MTHFR - methylenetetrahydrofolate reductase , PIH - pregnancy induced hypertension

but there was a difference in the HELLP syndrome group. In Chang et al[15] study only in the severe preeclampsia group revealed difference and in Paternoster et al[16] study only in preeclampsia group showed statistically significantly lower antithrombin III levels. We compared the protein C levels with other studies and found that there were significantly lower in the eclampsia group compared with the normotensive patients.[17,18] Heilmann et al[14] study could not find a statistically significant difference between the preeclampsia and control groups but there was a difference between the HELLP syndrome and the control groups. Paternoster et al[19] study also showed a statistically significant difference in patients with HELLP syndrome. There are also studies in the literature that show no statistically significant difference between the preeclamptic and normal patients for protein C levels.[20,21] Protein S results were not correlated with the majority of the literature. Because protein S levels were significantly higher in the chronic hypertension superimposed preeclampsia patients than the other subgroups, but there was no difference between the PIH and the control groups. In the literature, protein S levels were lower in the preeclampsia groups than the normotensive groups.[22,23] De Groot et al[21] study was correlated with our study and there was no statistically significance between the preeclamptic patients with the control group. Homocysteine levels were higher in eclampsia and eclampsia with HELLP syndrome and severe preeclampsia patients. Homocysteine levels in the PIH group were significantly higher than the control group. Other studies show similar results that the homocysteine levels are higher in the preeclampsia group than the normotensive patients,[24-28] but there are few studies that show there were no significant differences in the preeclampsia and normotensive patients.[29,30] Although Factor V Leiden mutation had a rate of 12% in the PIH group compared with 5% in the control group, which shows no significant difference.

There was no homozygote mutation for Factor V Leiden. Kim et al[31] reported no homozygote mutations, 6% in preeclamptic, 6.5% in severe preeclampsia, 4.54% in HELLP syndrome, and 4.7% in control patients. In our study the results were 11.1% (preeclamptic), 10% (severe preeclampsia), 20% (HELLP syndrome), and 4.9% (control patients). In most of the studies, they found none homozygote mutations and the results of the preeclamptic patients were not different than the control patients.[32-35] There are also studies which show difference between preeclampsia and the control groups.[5,8,36,37] In a recent meta-analysis, the pooled odds ratio (OR) for the association of Factor V Leiden and all cases of preeclampsia was 1.81 (95% confidence interval [CI] 1.14-2.87) and 2.24 (95% CI 1.28-3.94) for cases of severe preeclampsia.[7] For prothrombin 20210 mutation, in our study, we found no difference between the study group and the control group. Lin and August[7] meta-analysis the OR for the prothrombin 20210 polymorphism and all preeclampsia was 1.37 (95% CI 0.72-2.57) and 1.98 (.94-4.17) for severe preeclampsia.[7] When the PIH subgroups were evaluated for MTHFR 677 mutation there was a statistically significant difference, homozygote mutation was higher in chronic hypertension superimposed preeclampsia group and heterozygote mutation was noticed mostly in the eclampsia, severe preeclampsia and HELLP syndrome group. There was no significant difference between the control and the PIH groups. Our results were similar to Kim et al[31] study who reported homozygote mutation in preeclampsia 11.7%, severe preeclampsia 11.4% HELLP syndrome 9.5%, and 11.4% in the control group and there was no statistical significance regarding the groups. The ratio

of MTHFT 677 mutation was found no statistically significant difference between the PIH and control groups as has been observed in other studies.[6,30,32,38,39] In a recent meta-analysis the pooled OR for the MTHFR 677 genotype and all preeclampsia was 1.01 (95% CI 0.79-1.29) and 1.38 (95% CI 0.93-2.06) for severe preeclampsia.[7] There are also studies in which MTHFR 677 (both homozygote and also heterozygote) mutation was found to be statistically significantly higher than the control group.[40,41]

In conclusion, antithrombin III deficiency, protein C deficiency, hyperhomocysteinanemia were found to be associated with the PIH groups, but protein S deficiency, and homozygote Factor V Leiden mutation, prothrombin 20210, MTHFR 677 mutation were not found related with the PIH group.

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