P-selectin in pregnant women with vein thrombosis and compare the predictive value of this biomarker with Wells criteria

shervin tabrizian
Ardabil University of Medical Sciences: Ardebil University of Medical Sciences
hasan ghobadi
Ardabil University of Medical Sciences: Ardebil University of Medical Sciences
yadollah khorrami
Ardabil University of Medical Sciences: Ardebil University of Medical Sciences
masoomeh rostamnejhad
Ardabil University of Medical Sciences: Ardebil University of Medical Sciences
elham safarzadeh
Ardabil University of Medical Sciences: Ardebil University of Medical Sciences
somaieh matin (smh.matin@yahoo.com)
Ardabil University of Medical Sciences: Ardebil University of Medical Sciences

Research Article

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Abstract

Background: The diagnosis of venous thromboembolism (VTE) during pregnancy is a challenging task. Due to its naturally high level during pregnancy, D-Dimer concentration is not reliable diagnostic. P-selectin is another diagnostic biomarker that can aid the diagnosis of VTE. In the present study, an attempt was made to determine the relationship between P-selectin and acute VTE in pregnant women and compare it's predictive value with Wells criteria.

Materials and methods: In this case-control study, 29 pregnant women with pulmonary thromboembolism (PTE), 33 pregnant women with deep vein thrombosis (DVT), and 32 matched healthy pregnant women were investigated. After obtaining informed written consent, 3 cc of venous blood sample was taken from each of the participants. The samples were then assessed for P-selectin and D-Dimer concentrations via the use of ELISA tests. Finally, statistical analyses were performed.

Findings: Significant differences were observed between all of the groups under investigation in terms of both mean P-selectin and mean D-Dimer concentrations ($P<0.05$). The mean P-selectin concentration in patients with high Wells score was significantly higher than that of the patients with moderate and low Wells score ($P<0.05$). Moreover, week positive correlation was observed between P-selectin and D-Dimer concentrations ($r=0.3$, $P=0.003$). Logistic regression also revealed that both P-selectin and D-dimer were predictive factors of thrombosis in pregnant women.

Conclusion: The increase in P-selectin concentration during pregnancy is associated with high incidence of VTE. Compared with D-Dimer, P-selectin is a predictor of thrombosis, especially in patients with high clinical probability based on Wells score.

Introduction

Venous thromboembolism (VTE) is one of the preventable causes of death during both pregnancy and the postpartum period. It can also cause lifelong disability in the afflicted patients (1). The probability of this condition in the pregnant women as well as in those who are in the postpartum period is 4 to 50 times higher as compared to other normal women in the same age group (2). VTE can occur anytime during pregnancy, and its probability is even higher during the first 6 weeks after delivery (3). Since its symptoms overlap with the natural symptoms of pregnancy, the diagnosis of VTE during this period has proved to be a challenging task. D-Dimer is generally considered as a predictive factor for thrombosis. However, due to its natural increase as the result of pregnancy, D-Dimer concentration is of less value in the diagnosis of thrombosis in pregnant women (4). Therefore, other biomarkers need to be considered for the diagnosis of this condition during pregnancy.

Serum P-selectin level can be one of the alternative diagnostic biomarkers for VTE. As the mediator for the adhesion of leukocytes to vascular endothelial cells, this biomarker has attracted the attention of numerous researchers (5). P-selectin is stored in platelet α–granules and Weibel-Palade bodies of endothelial cells and is rapidly translocated to the cell surface during inflammatory responses (5). The

relationship between inflammation and venous thrombosis has been illustrated well in Virchow's Triad (6). An inflammatory response in the body can result in VTE (7). Various studies have shown that P-selectin level increases as the result of inflammation and acute venous thrombosis (8, 9). It has also been reported that elevated levels of P-selectin can be associated with the recurrence of VTE and the development of thrombosis (7). Recently, some studies have reported high levels of this protein in recurrent venous thromboses associated with cancer (10, 11). Regarding the relatively high prevalence of VTE and its various complications during pregnancy, the present study aimed to determine the predictive capacity of serum P-selectin in the diagnosis of VTE in the pregnant women clinically suspected of this condition.

Methods

This study was conducted on 3 groups of women in Imam Khomeini Hospital in Ardabil during 2019-2020. More specifically, 29 pregnant women definitively diagnosed with pulmonary thromboembolism (PTE), 33 pregnant women definitively diagnosed with deep vein thrombosis (DVT), and 32 matched healthy controls (who had no thrombosis symptom) were investigated. The inclusion criteria in the study were being diagnosed with thrombosis based on color doppler ultrasound image and being diagnosed with embolism based on pulmonary ventilation/ perfusion scan. The exclusion criteria, on the other hand, were being afflicted with chronic diseases such as hypertension, cardiovascular diseases, infections of any type, and preeclampsia.

The participants in the control group were matched with those in the case groups in terms of maternal age and gestational age. Before beginning the investigation, a written informed consent was obtained from each of the participants. Then using a checklist developed by the researchers, the patients' demographic information, their gestational age, and the presence of risk factors for thrombosis in them were recorded. After that, 3 cc of venous blood sample was taken from each of the participants for the assessment of serum P-selectin and serum D-Dimer concentrations. The obtained blood samples were kept at room temperature for 15 to 30 minutes. Then they were centrifuged for 10 to 15 minutes at the speed of 2500-300 rpm to separate serum from the blood. After that, P-selectin and D-Dimer levels were checked with ELISA tests, and the obtained results were recorded in the checklists.

In the final stage, the collected data were all fed into SPSS Software, Version 25, and the needed analyses were performed using descriptive statistics, independent t-test, Kruskal-Wallis, Mann-Whitney U, Chi square, Fisher's exact test, and logistic regression. The significance level for all of the tests was set at $P<0.05$. The current study was approved in the Research Ethics Committee of Ardabil University of Medical Sciences with the code of IR.ARUMS.REC.1397.306.

Findings

In this study, 33 pregnant women with PTE, 29 pregnant women with DVT, and 32 matched healthy controls were investigated.

The three groups under investigation were not found to be significantly different in terms of maternal age, gestational age, and Body Mass Index (BMI) (Table 1).

Table 1
Comparison of age, body mass index and gestational age variables in the study groups

	DVT group n=29	PTE group n=33	Control group n=32	
Age	27.9±6.4	29.7±6.2	26.9±5.4	P=0.18
BMI	27.3±3.9	28.7±3.1	28.8±4.8	P=.28
Gestational age	27.5±7.2	27.7±7.1	27.7±7.8	P=0.99

As for the risk factors for thrombosis and embolism, the analyses indicated no significant differences among the three groups regarding history of thrombosis, history of trauma, and consumption of contraceptive pills (Table 2).

Table2: Distribution of study groups in terms of thrombosis risk factors

Variable	DVT group n=29	PTE group n=33	Control group n=32	P value
Recent surgical history	11(37.9%)	20(60.6%)	18(56.3%)	0.17
history consumption of contraceptive	6(20.7%)	8(24.2%)	14(43.8%)	0.09
History of trauma	1(3.4%)	2(6.1%)	0(0%)	0.37

However, the three groups turned out to be significantly different in terms of the mean serum levels of D-Dimer and P-selectin.

Table 3
Mean laboratory variables of the subjects by groups

variable	DVT group n=29	PTE group n=33	Control group n=32	P value
Didimer	1116.45±845	1026.61±674	609.38±401	0.007
p-selectin	296.93±159	397.06±127	189.91±108	<0.001

Patients with DVT were further subdivided into two subgroups. One subgroup included patients with low or moderate probability of being afflicted with VTE based on their Wells score, and the other subgroup consisted of those with high probability of being afflicted with VTE again based on their Wells score. The analysis of these two subgroups revealed that P-selectin level was significantly higher in patients with

high Wells score as compared to the other subgroup. Patients with PTE were also subdivided into two subgroups in the same way as DVT patients. In this case, however, no significant difference was observed between the two subgroups in terms of P-selectin level (P=0.8) (Table 4).

Table 4
Comparison of p-selectin levels by wells score in two groups of patients with DVT and PTE

Groups	wells score	N	Mean±SD	p-value
DVT	low probability	26	275.81±123	0.03
	Medium and high probability	3	480.00±329	
PTE	low probability	6	382.17±116	0.8
	high probability	27	400.37±131	

The comparison of the three groups under investigation in different trimesters of pregnancy indicated that P-selectin level in the group of patients with PTE was higher than that of the other groups in all trimesters.

The results also demonstrated a positive correlation between P-selectin and D-Dimer levels (r=0.3, P=.003).

Moreover, logistic regression indicated that from among the factors associated with the incidence of thrombosis, P-selectin and D-Dimer were the only predictive factors for thrombosis in the pregnant women.

	B	S.E.	Sig.
Ddimer	.001	.000	.039
Pselectin	.008	.003	.001
Oral cotraceptive	.832	.593	.160
Welse in PTE group	-1.060	.647	.101
Welse in DVT group	.680	1.295	.600
Constant	-3.182	1.588	.045

Discussion

The results of the current study indicated that P-selectin concentration was significantly higher in the group of patients with thrombosis as compared to the healthy controls. The three groups under investigation were found to be significantly different in terms of mean D-Dimer and mean P-selectin concentrations. The results also demonstrated a positive correlation between P-selectin and D-Dimer

levels in the pregnant women. Moreover, logistic regression revealed that from among the factors associated with the incidence of thrombosis, P-selectin and D-Dimer were the good predictive factors for thrombosis in the pregnant women. Finally, it was observed that high Wells score was associated with higher levels of P-selectin.

Thrombosis and embolism mainly occur during pregnancy and the postpartum period. Their incidence rate is particularly high during the postpartum period. P-selectin plays a key role in the pathophysiology of thrombosis. The effects of the high level of soluble P-selectin (sP-selectin) on VTE have not been determined yet. Some researchers have explored the relationship between sP-selectin and VTE. Some others have assessed sP-selectin as a predictive factor for acute thrombosis. The results, however, are mixed and inconsistent.

P-selectin is expressed on the surface of activated platelets and endothelial cells. It has been reported to trigger the adhesion of platelets to monocytes and neutrophils. This protein is rapidly translocated from the surface of the platelet membrane and appears in the form of a solution in the blood flow. P-selectin plays a key role in the initial recruitment of leukocytes into the site of injury or inflammation. Several studies have reported inflammation as the cause of thrombosis (6).

In a case-control study conducted by Ay et al., 116 patients suffering from recurrent VTE and 129 healthy controls were investigated. The results indicated that the mean P-selectin level was higher in the case group as compared to the control group. They also found that the risk of elevated sP-selectin concentration was considerably high in patients with VTE. They observed no significant relationship between sP-selectin concentration and platelet count or BMI. Their findings also demonstrated that the increase in sP-selectin concentration played a similar or even more important role than the increase in factor VIII level, hyperhomocysteinemia, and factor V Leiden mutation in VTE (12). The findings reported in that study are consistent with the findings of the current study.

In their study, Rectenwald et al. introduced P-selectin as a new and important predictive factor for DVT (13). In another study, Smith et al. investigated three groups of participants: patients with spontaneous venous thrombosis, patients with postoperative thrombosis, and a group of healthy controls. Their findings indicated that P-selectin level was strongly correlated with thrombosis and could be used as a prognostic factor for determining the risk of thrombosis after surgery (14). The findings reported in both of these studies are in line with the findings of the present study.

In the study conducted by Bucek et al., patients with VTE did not show any significant difference from the healthy controls in terms of sP-selectin concentration (15). This finding is not in line with our findings in the current study. This inconsistency might be due to the differences in the statistical population addressed in each study as well as the duration of investigation.

According to the results obtained in the current study, P-selectin level was not associated with gestational age. In a different study, Bioso et al. assessed plasma P-selectin levels during pregnancy with the aim of determining its impact on hypertension and preeclampsia in the pregnant women. They observed that in

none of the stages of pregnancy was there any significant difference between the case group and the control group as regards P-selectin level (16). Although the statistical population of their study was different from ours, the findings of the two studies are consistent.

Conclusion

The results of the present study revealed that P-selectin concentration increased in the pregnant women afflicted with thrombosis. Compared with other biochemical and clinical risk factors (e.g., D-Dimer, and Wells score, respectively), this biomarker is a stronger predictor of thrombosis. It seems that this marker can be used to recognize women at high risk of thrombosis. However, to further verify the findings of this study, it is suggested that similar studies with larger sample sizes be conducted.

Declarations

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Compliance with Ethical Standards

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Conflict of Interest: The authors declare that there is no conflict of interest.

Informed consent: Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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Figures

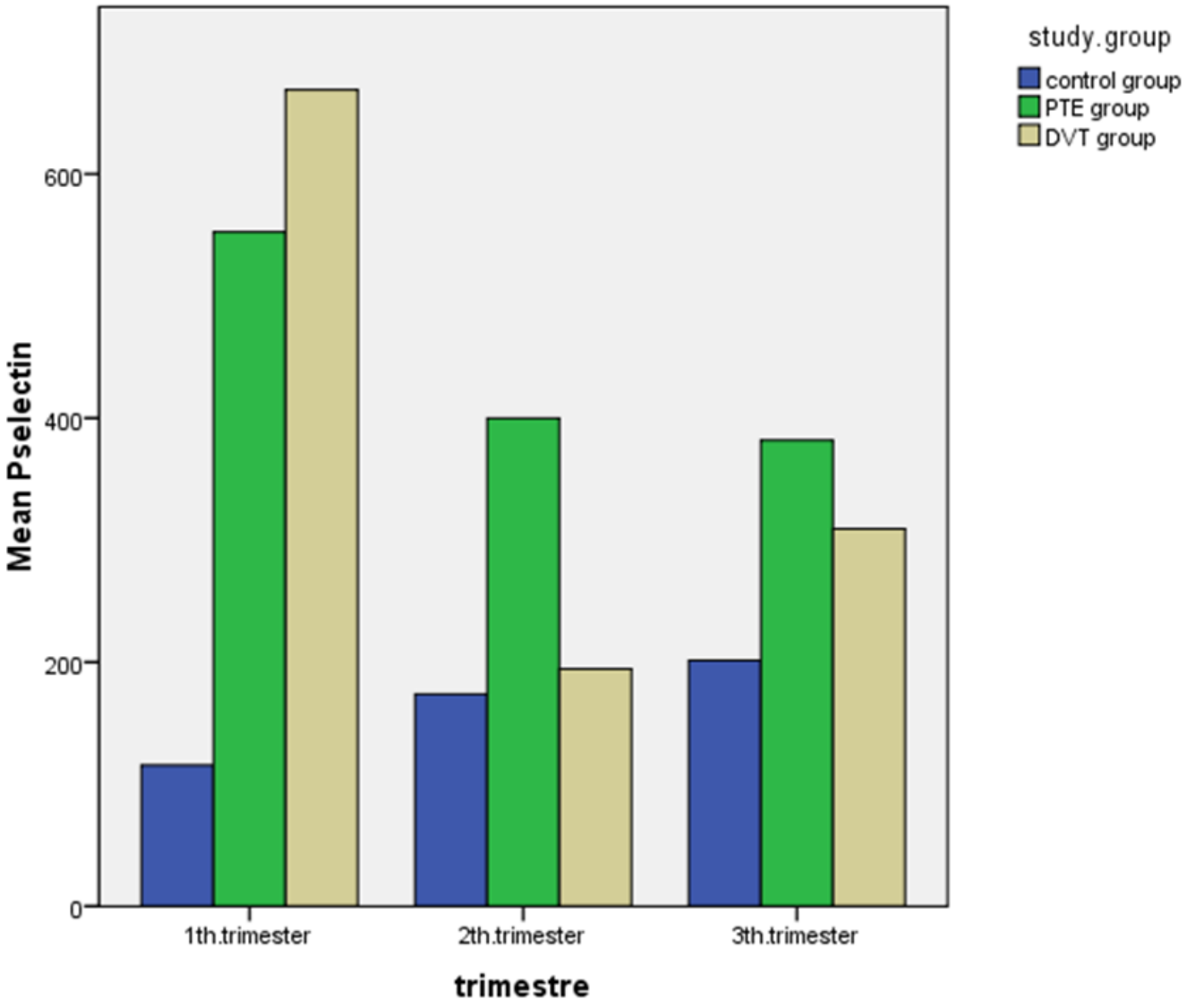

Figure 1

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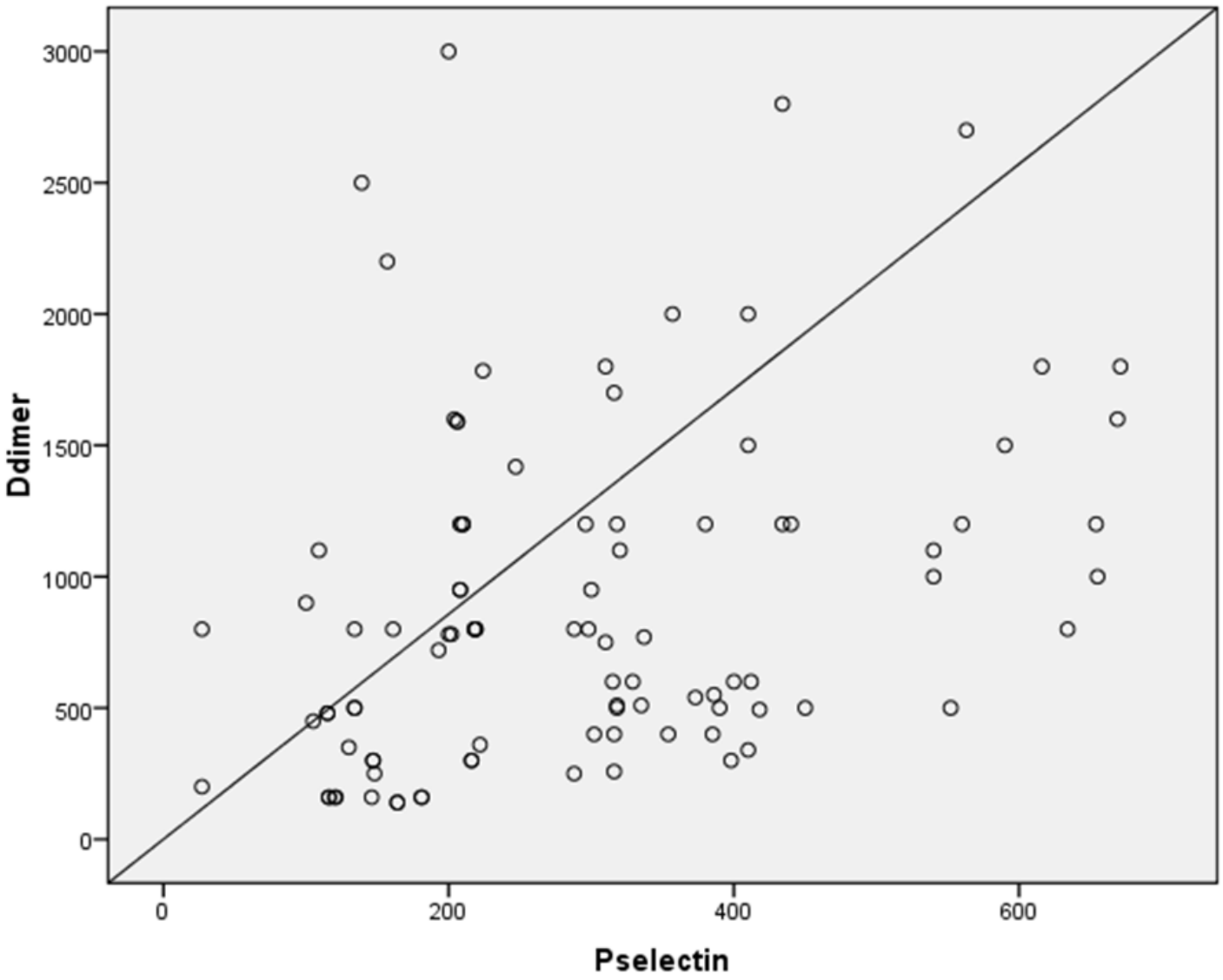

Figure 2

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