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Original Article

The Optimal Cutoff Level of D-Dimer during Pregnancy to Exclude Deep Vein Thrombosis, and the Association between D-Dimer and Postpartum Hemorrhage in Cesarean Section Patients

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Summary: ***Objective*****:** The main purpose was to clarify the optimal D-dimer cutoff level during pregnancy to exclude deep vein thrombosis (DVT) prior to Cesarean section. The secondary purpose was to determine whether D-dimer can predict severe postpartum hemorrhage (PPH) in Cesarean section patients.

Methods**:** Two hundred and seventy eight elective Cesarean section cases were enrolled. Clinical factors and blood parameters at 34-37 weeks of gestation were analyzed. To detect DVT, lower extremities veins were examined using color Doppler ultrasonography in cases with D-dimer level $\geq$ 1.5 μg/mL. In addition, postpartum blood loss amounts during Cesarean section were recorded.

Results**:** Five DVT cases occurred in 250 singleton pregnancies, and 2 DVT cases occurred in 28 twin pregnancies. The overall incidence of DVT was 2.5%. The D-dimer level was higher in DVT cases than in non-DVT cases (3.84±1.97 vs. 2.31±1.48 μg/mL, P<0.01). The optimal D-dimer cutoff level was 2.6 μg/mL with a negative predictive value of 99.5%, and sensitivity of 85.7%. PPH during Cesarean section was positively correlated with D-dimer level in all pregnancies. However, this relationship disappeared after excluding twin pregnancies.

Conclusion**:** A D-dimer level < 2.6 μg/mL at 34-37 weeks of gestation has the potential to exclude DVT. D-dimer can be an independent predictor for severe PPH for all Cesarean section cases, including twin pregnancies.

Key words D-dimer, deep vein thrombosis, cutoff level, singleton, twin pregnancies, postpartum hemorrhage

INTRODUCTION

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE). In pregnancy-associated VTE cases, approximately 75-80% are DVT, and 20-25% are PTE cases [1-4]. PTE caused by DVT is the leading cause of morbidity and mortality during pregnancy. In the general population, risk factors for VTE are age, morbid obesity, cancer and its treatment, prolonged immobility, long air travel, dehydration, and long-time operative surgery. In the obstetric field, VTE risk factors include pregnancy, Cesarean section, puerperium, long-term immobility by long hospitalization due to obstetrical disease such as threatened premature labor. The incidence of DVT is estimated to be 0.76 to 1.72 per 1,000 pregnancies. The risk is 4-5 fold higher than that in the non-pregnant population [1,5]. Thus, prompt and accurate diagnosis of DVT as the prestage of PTE is of utmost importance to prevent PTE during pregnancy.

D-dimer levels have high negative predictive val-

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Abbreviations: APTT, activated partial thromboplastin time; ART, assisted reproductive technology; BMI, body mass index; DVT, deep vein thrombosis; Hb, hemoglobin; Ht, hematocrit; Plt, platelet counts; PPH, postpartum hemorrhage; PTE, pulmonary thromboembolism; PT-INR, prothrombin-international normalized ratio; ROC, receiver operating characteristic; SD, standard deviation; VTE, venous thromboembolism ue for excluding DVT in the general population [6,7]. As for pregnant women, a higher cutoff D-dimer level has been proposed due to its continuous increase throughout pregnancy and puerperium. However, the optimal cutoff D-dimer level to exclude DVT during pregnancy remains unclear [8-12]. Though D-dimer cutoff level to exclude symptomatic DVT has been reported, there are few reports on the optimal cutoff level to exclude even asymptomatic DVT to prevent postoperative PTE. In addition, severe postpartum hemorrhage (PPH) is a major cause of maternal death [13]. A few reports are available suggesting that the D-dimer level during pregnancy could be a predictor for PPH [14].

The purpose of this study was to clarify the optimal cutoff level of D-dimer to exclude both symptomatic and asymptomatic DVT prior to elective Cesarean section, and the association of D-dimer with severe PPH in Cesarean section patients. Reasons why elective Cesarean section was selected in our study are that the DVT incidence is significantly higher in Cesarean section cases than vaginal delivery cases [15-17], and D-dimer is generally measured as a pre-operative laboratory examination just before elective Cesarean section.

MATERIALS AND METHODS

This retrospective cohort study was conducted in accordance with the IRB at Kanoya Medical Center and the 2013 Declaration of Helsinki. Subjects were restricted to patients who underwent elective Cesarean section. We collected data from 279 Cesarean section cases between May 2013 and November 2017 at the Department of Obstetrics and Gynecology, Kanoya Medical Center. One patient with antiphospholipid antibody syndrome was excluded.

The number of enrolled pregnant women was 278 including 206 cases (74.1%) with ultrasonography screening for DVT. Veins in the lower extremities were examined for DVT using color Doppler ultrasonography by experienced cardiologists. Patients with a D-dimer level under 1.5 μg/mL were not examined for DVT by ultrasonography, because the Ultrasonography Department in our hospital confirmed, based on evaluation of a great many cases, that no patients had DVT, including asymptomatic DVT, when DVT < 1.5 μg/mL. As a result, 250 singleton pregnancies including 5 DVT cases and 28 twin pregnancies including 2 DVT cases were enrolled in this study.

Our protocol for preventing VTE in pregnant women is as follows. All patients wear elastic stockings, postoperative early mobilization, intermittent pneumatic compression of the lower limbs and anticoagulant therapy as appropriate, and walk one day after operation. In the case of DVT detection before Cesarean section, we usually treat DVT using intravenous unfractionated heparin injection (10,000 unit/day) until six hours before operation, and restart 12hours after operation. Thereafter, we replace heparin by warfarin. Patients with symptoms of PTE were examined by enhanced computed tomography for accurate diagnosis.

Baseline characteristics included age, smoking status, gravidity, history of spontaneous abortion, current history of assisted reproductive technology (ART), number of fetuses, hospitalization due to threatened premature labor. Body mass index (BMI), blood pressure, and clinical blood parameters were all measured during 34–37 weeks of gestation as pre-operative examinations prior to Cesarean section. BMI was calculated as the weight (kg) divided by height squared (m^2). Clinical blood parameters included the D-dimer level, prothrombin-international normalized ratio (PT-INR), activated partial thromboplastin time (APTT), and hemoglobin (Hb), hematocrit (Hct), and platelet counts (Plt). The D-dimer level was assayed using latex immunology nephelometry methods (range 0.0–30.0 μg/mL). As for PPH, blood loss amounts during Cesarean section including amniotic fluid were measured.

At first, the relationship of DVT with various clinical factors was analyzed to confirm the validity of D-dimer as a predictor of DVT. Next, the relationship of D-dimer level with other variables was analyzed. The highest sensitivity-(1-specificity) among the D-dimer levels of the cases with DVT was determined as the optimal cutoff level. Negative and positive predictive values, sensitivity, and specificity were compared among the optimal cutoff level and its neighboring cutoff levels. Receiver Operating Characteristic (ROC) analysis was performed between D-dimer and DVT. In addition, we investigated whether or not postpartum blood loss during Cesarean section was associated with the D-dimer level.

As for statistical analysis, inter-group comparisons were made using Student's *t*-test for continuous variables (age, gravidity, BMI, blood pressure, blood parameters and blood loss in Cesarean section) or Chi-square test for nominal variables (smoking status, history of spontaneous abortion, ART, hospitalization). Relationships between two variables were investigated using univariate regression analysis. In regression analyses, the independent variable was D-dimer level or DVT. As for a nominal variable of DVT, its presence and absence were registered as 1 and 0, respectively. The other nominal variables were registered in the same way as DVT. Other continuous variables, including clinical factors and blood parameters, were independent variables. Data were expressed as the mean ± standard deviation (SD), percentage, or fraction, as appropriate. $P<0.05$ was considered significant.

RESULTS

The overall incidence of DVT during pregnancy just before elective Cesarean section was 7 cases per 278 pregnancies (2.5%), including 5 cases per 250 singleton pregnancies (2.0%), and 2 cases per 28 twin pregnancies (7.1%). As shown in Table 1, DVT was found in the bilateral soleus muscle vein (n=2), right peroneal vein (n=1), bilateral superficial femoral veins (n=1), right superficial femoral vein (n=1), and left soleus muscle vein (n=2). There was no significant laterality. No DVT cases had developed into PTE at one month after cesarean section. Various clinical factors were compared in pregnant women with DVT (n=7) and without DVT (n=271) (Table 2). The incidence of hospitalization due to threatened premature labor was higher ($P<0.01$). However, other clinical factors did not differ between the two groups. The D-dimer level was significantly higher in women with DVT than in those without DVT (3.84±1.94 vs. 2.31±1.48 µg/mL, $P<0.01$, Figure 1). Other hemostatic parameters did not differ between the two groups.

Since twin pregnancy is generally reported as one of the risk factors for DVT, comparisons of clinical factors and blood parameters between singleton and twin pregnancies were analyzed (Table 3). Age, Hb and Hct were significantly higher in singleton pregnancies, and the incidences of current history of ART, hospitalization due to the threatened premature labor, D-dimer level and PPH were significantly higher in twin pregnancies. Blood loss by PPH in twin pregnancies was twice that in singleton pregnancies.

The univariate regression analysis for the incidence of DVT in all cases is presented in Table 4. Hos-

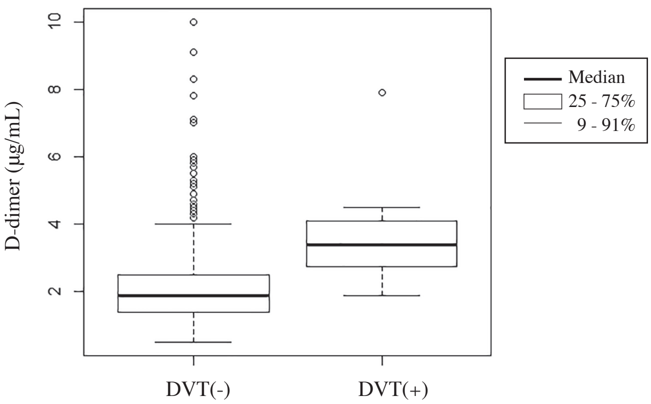

Fig. 1. Distribution of D-dimer levels in the patients with or without DVT.
D-dimer level differs significantly between negative DVT group (n=271) and positive DVT group (n=7). $P < 0.01$

TABLE 1.
Profiles of 7cases with DVT

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age (years)	42	27	27	38	34	34	34
Symptoms	none	none	leg edema	none	none	none	none
DVT side	bilateral	right	bilateral	right	left	left	left
Region	soleus muscle vein	peroneal vein	soleus muscle vein	superficial femoral vein	soleus muscle vein	soleus muscle vein	peroneal vein
D-dimer* (µg/mL)	1.9	2.6	3.4	3.7	4.5	2.9	7.9
Smoking	-	+	-	-	-	+	-
Fetal number	1	1	1	1	1	2	2
Hospitalization due to the threatened premature labor	-	+	-	-	+	+	+

*Measured during 34-37 weeks of gestation pitalization due to threatened premature labor and D-dimer level were significantly correlated with DVT($P<0.01$), but no other factors were correlated. In the cases of singleton pregnancy, only the D-dimer level positively correlated with DVT ($P<0.05$). The outcomes of the univariate regression analysis for the D-dimer level in variables are presented in Table 5. ART, hospitalization due to threatened premature labor and PPH were positively correlated with the D-dimer level, but Hb and Hct were inversely correlated. As for singleton pregnancies, maternal age and hospitalization due to threatened premature labor were positively correlated with D-dimer level, whereas Hb and Hct were inversely correlated.

The key points of the ROC curve (Figure 2), and relationships between D-dimer level and DVT are summarized in Table 6. A D-dimer level of 2.6 μg/mL had the highest sensitivity-(1-specificity) and was set as the optimal cutoff level during pregnancy. The cutoff level of 2.6 μg/mL was superior to its neighboring cutoff levels of 1.9 and 2.9 μg/mL in terms of negative and positive predictive value, respectively.

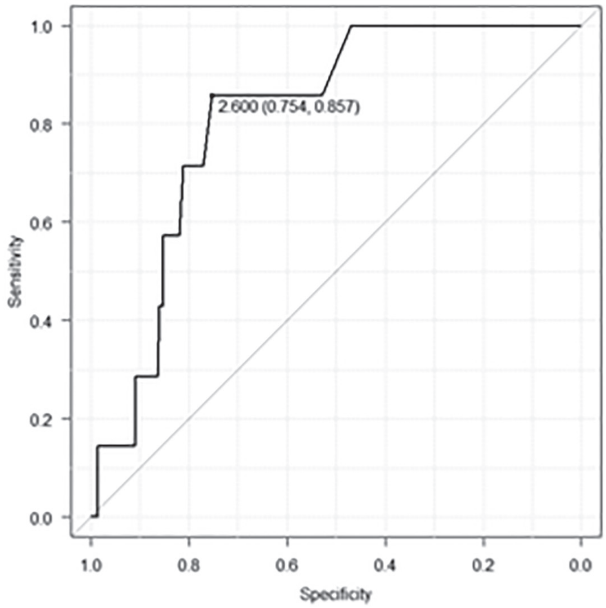

Fig. 2. ROC curve between D-dimer level and the incidence of DVT.
ROC analysis was performed for D-dimer level and DVT incidence. Area under the curve is 0.744 (95%CI=0.582 to 0.906).

TABLE 2.
Comparisons of clinical factors and blood test results in pregnant women with and without DVT

	DVT(+) (n=7)	DVT(-) (n=271)	*P*-value
Age (years)	33.7±5.4	32.9±5.2	N.S.
Smoker (%)	28.6	11.1	N.S.
Gravidity	1.00±0.82	1.72±1.42	N.S.
History of spontaneous abortion (%)*	14.3	27.2	N.S.
Assisted reproductive technology (%)*	28.6	14.0	N.S.
Hospitalization due to the threatened premature labor (%)*	57.1	17.6	<0.01
Body mass index**	27.1±5.9	27.2±4.8	N.S.
Systolic blood pressure (mmHg)**	113.7±8.4	113.7±12.8	N.S.
Diastolic blood pressure (mmHg)**	67.1±5.4	66.5±11.0	N.S.
D-dimer (μg/mL)*	3.84±1.97	2.31±1.48	<0.01
PT INR**	1.03±0.07	1.01±0.06	N.S.
APTT (seconds)**	28.4±3.3	28.5±3.3	N.S.
Hb (g/dL)**	10.3±0.93	10.8±1.03	N.S.
Hct (%)**	31.8±2.88	33.0±2.83	N.S.
Plt ($\times 10^4$/μL)**	24.0±5.23	23.8±6.22	N.S.
Postpartum hemorrhage (mL)*	1036±356	1064±592	N.S.

*Related with the present pregnancy
**Measured during 34-37 weeks of gestation

The D-dimer level at 34-37 weeks of gestation was positively correlated with PPH during Cesarean section (Table 5). However, this relationship disappeared after excluding twin pregnancies from the correlation test. But there was a tendency for the average D-dimer to be elevated in accordance with blood loss. Even in singleton pregnancies, the average D-dimer levels were 2.10 μg/ mL in cases with blood loss under 1,000 mL, 2.17 μg/mL with blood loss of 1,000-1,500 mL, 2.33 μg/mL with blood loss of 1,501-2,000 mL, and 2.49 μg/mL over 2,000 mL.

DISCUSSION

DVT may be clinically suspected using rules such as Wells' criteria [7]. Diagnosis is most commonly performed with Doppler ultrasonography of the suspected veins. Elevation of the D-dimer level assists in finding DVT, because of its high sensitivity and high negative predictive value. Many studies have reported that the D-dimer level in combination with clinical assessment of the non-pregnant population is useful to exclude DVT [7,18]. Therefore, the D-dimer level is often used to exclude not only symptomatic but also asymptomatic DVT before surgery. Indeed, the incidence of symptomatic DVT during pregnancy is much lower than that of asymptomatic DVT (0.054%–0.76%) [5,17]. In our study, 6 of 7 cases with DVT were asymptomatic. Therefore, screening for DVT based on D-dimer level before elective Cesarean section is useful to prevent postpartum PTE. However, the D-dimer level continuously increases throughout pregnancy because of hypercoagulability and the compression of intra-pelvic blood vessels by the enlarged pregnant uterus. Hypercoagulability increases the levels of pro-coagulant factors and decreases anticoagulant activity, protecting pregnant women from fatal PPH, but pre-disposing them to thromboembolism. Pregnancy-specific references for D-dimer ranges have been proposed in healthy pregnant women [19-22]. A new cutoff level for the D-dimer level to exclude DVT was suggested for each trimester [10,25]. However, the optimal D-dimer cutoff level to exclude DVT during pregnancy remains unestablished [11,12,17]. Although asymptomatic DVT rarely causes PTE, it is important to be aware of the existence of DVT even if small or distal. The present study identified a D-dimer cutoff level that included asymptomatic DVT.

In this study, we examined veins in the lower extremities for DVT using color Doppler ultrasonography in pregnant women whose D-dimer levels were ≥ 1.5 μg/mL at the third trimester. None of the cases developed into PTE during the study period. The overall incidence of DVT during the perinatal period was 2.5% (7/278), consistent with previous reports [24]. This result was obtained after excluding women with vaginal deliveries, so that the incidence of DVT in all pregnancies may be lower than 2.5%. A population-based cohort study in Canada found that the incidence of DVT during pregnancy was 0.12% [5]. In contrast, Nishii et al [21] reported a 5.0% (54/1078) DVT incidence in Japanese pregnant women. The reasons for this discrepancy include differences in study design, methods and skill of DVT detection, clinical factors, residential regions, hospital scale, and the sample size, etc. The ratio of twin pregnancies is also one reason, because twin pregnancy itself has a higher risk of DVT than singleton pregnancy[25].

In our study, the mean D-dimer level at 34-37 weeks of gestation was 3.84 μg/mL in DVT cases, which was significantly higher than 2.31 μg/mL in non-DVT cases. This result is consistent with previous reports [19,21]. However, the D-dimer level in twin pregnancies differs among reports. At the third trimester, we found that the D-dimer level was significantly higher in twins than in singletons (Table 4). The difference in D-dimer level between single and twin pregnancies may become evident at the third trimester. Increased D-dimer level in twin pregnancies may be due to the enlarged pregnant uterus, which compresses pelvic blood vessels, and to reduced maternal daily activity. The higher D-dimer level in twin pregnancies is in agreement with the finding that the risk of DVT continues throughout pregnancy and becomes highest at the postpartum period. The incidence of DVT was also higher in twin pregnancies [9,21,25].

Since hospitalization due to threatened premature labor increases the DVT risk, especially in cases of prolonged hospitalization, prevention of DVT by such methods as wearing elastic stockings and frequent lower limb exercise is important. In addition, it is also important to reduce unnecessary hospitalization and bed rest.

We concluded the optimal D-dimer cutoff level to be 2.6 μg/mL in the third trimester of the pregnant women. On the other hand, Nishii et al. [21] concluded the optimal cutoff level to be 3.2 μg/mL. In their study, the positive and negative predictive value of 3.2 μg/dL was 7.4% and 95.5%, respectively. Although the positive predictive value was low, the diagnostic accuracy of D-dimer levels for excluding DVT was reasonably good. From the point of view that the optimal cutoff level is more useful as a negative predictor for DVT, our cutoff level of 2.6 μg/mL had the better negative predictive value of 99.5%. The difference in optimal cutoff levels between other studies and ours may be due to the difference in background, including life style, race, and ratio of twin pregnancies. Considering these findings, pregnant women with DVT show an increase in D-dimer level that exceeds the normal continuous physiological increase during pregnancy. Although it is true that the D-dimer level exhibits diagnostic accuracy for VTE during pregnancy, the elevation in D-dimer levels due to DVT may be masked by a higher physiological increase in the D-dimer level during pregnancy. Nevertheless, we concluded that D-dimer level has enough power to exclude asymptomatic DVT before elective Cesarean section.

PPH is a major cause of maternal mortality, along with PTE. Only limited data are available regarding the relationship between the D-dimer level and PPH [13,14]. Whether the D-dimer level is associated with PPH is of interest. We found that the D-dimer level at 34-37 weeks of gestation was positively correlated with PPH in all Cesarean section cases. However, this relationship disappeared after excluding twin pregnancies. In the present study, twin pregnancies had a greater incidence of PPH than singleton pregnancies (Table 3). Previous reports demonstrated by univariate analysis that severe PPH is associated with a higher D-dimer level during pregnancy [14], but this relationship disappeared in singleton pregnancies in our study (Table 5). Although no significant relationship between D-dimer level and PPH was confirmed, D-dimer level tended to increase along with blood loss. Further examination will be needed to clarify the relationship between D-dimer level and PPH. D-dimer elevation is thought to reflect enhanced fibrinolysis, i.e. consumption of fibrinogen leading to lower fibrinogen level. This is the main mechanism to explain the correlation between D-dimer and PPH [14].

CONCLUSION

D-dimer and long hospitalization are independent risk factors for DVT. However, in this study the latter lost statistical significance in the case of singleton pregnancies. The D-dimer level physiologically increases with advancing gestational age, and this increase is more evident in twin pregnancies. Although the increase in D-dimer level by DVT may be masked by physiological increases, D-dimer level less than 2.6 μg/mL may sufficiently exclude DVT prior to elective Cesarean section at 34-37 weeks of gestation. As for PPH, D-dimer level and twin pregnancy seem to be risk factors. We should pay attention not only to DVT but also to severe PPH, especially in twin pregnancies

TABLE 3.
Comparison of background between singleton and twin pregnancies

	singleton (n=250)	twin (n=28)	*P*-value
Age (years)	33.3 ± 5.2	30.2 ± 3.6	<0.01
Smoker (%)	12.0	25.0	N.S.
Assisted reproductive technology (%)	11.6	39.3	<0.001
Hospitalization due to the threatened premature labor (%)	12.8	78.6	<0.01
Body mass index	27.2 ± 4.9	26.8 ± 4.0	N.S.
Systolic blood pressure (mmHg)	113.4 ± 12.6	116.4 ± 13.0	N.S.
Diastolic blood pressure (mmHg)	66.3 ± 10.9	67.8 ± 11.2	N.S.
D-dimer (μg/mL)	2.10 ± 1.11	4.64 ± 2.44	<0.01
PT INR	1.01 ± 0.06	1.01 ± 0.05	N.S.
APTT (seconds)	28.4 ± 3.2	29.2 ± 4.3	N.S.
Hb (g/dL)	10.9 ± 1.02	10.2 ± 0.88	<0.01
Hct (%)	33.2 ± 2.82	31.7 ± 2.67	<0.01
Plt ($\times 10^4$/μL)	24.0 ± 6.26	22.6 ± 5.43	N.S.
Postpartum hemorrhage (mL)	976 ± 463	1839 ± 931	<0.01

TABLE 4.
Univariate regression analysis for DVT incidence

	Regression coefficient	
	all (n=278)	singleton (n=250)
Age (years)	0.00071	0.0024
Smoker	0.033	0.0014
Hospitalization due to the threatened premature labor	0.064**	0.053
Body mass index	<−0.0001	0.0014
Systolic blood pressure (mmHg)	<−0.0001	−0.00026
Diastolic blood pressure (mmHg)	0.00014	−0.0026
D-dimer (μg/mL)	0.0165**	0.018*
PT-INR	0.16	0.15
APTT (seconds)	−0.00029	0.00084
Hb (g/dL)	−0.0013	−0.013
Hct (%)	−0.0039	−0.0043
Plt ($\times 10^4$/μL)	<−0.001	0.00063
Postpartum hemorrhage (mL)	<−0.001	<0.0001

$*P < 0.05$, $**P < 0.01$

TABLE 5.
Univariate regression analysis for D-dimer level

	Regression coefficient	
	all (n=278)	singleton (n=250)
Age (years)	0.039	0.029*
Smoker	−0.45	−0.29
Assisted reproductive technology	0.95***	−0.057
Hospitalization due to the threatened premature labor	1.7***	0.69**
Body mass index	−0.026	0.052
Systolic blood pressure (mmHg)	−0.0074	−0.011
Diastolic blood pressure (mmHg)	−0.0058	−0.011
PT-INR	−1.9	−1.7
APTT (seconds)	−0.032	−0.029
Hb (g/dL)	−0.30***	−0.16*
Hct (%)	−0.11***	−0.071**
Plt ($\times 10^4$/μL)	−0.012	−0.010
Postpartum hemorrhage (mL)	0.0011***	0.00026

$*P < 0.05$, $**P < 0.01$, $***P < 0.001$

TABLE 6.
Relationship between D-dimer cutoff levels and the incidence of DVT

D-dimer (μg/dL)	NPV	PPV	Sensitivity	Specificity	1-specificity	Sensitivity-(1-specificity)
1.9	100% (128/128)	4.7% (7/150)	100% (7/7)	47.2% (128/271)	0.528	0.472
2.6	99.5% (205/206)	8.3% (6/72)	85.7% (6/7)	75.4% (205/271)	0.246	0.611
2.9	99.1% (221/223)	9.1% (5/55)	71.4% (5/7)	81.3% (221/271)	0.187	0.53
3.4	98.7% (232/235)	9.3% (4/43)	57.1% (4/7)	85.3% (232/271)	0.147	0.424
3.7	98.3% (233/237)	7.3% (3/41)	42.9% (3/7)	85.7% (233/271)	0.143	0.286
4.9	98.1% (254/259)	10.5% (2/19)	28.6% (2/7)	93.4% (254/271)	0.066	0.22
7.9	97.8% (268/274)	25.0% (1/4)	14.3% (1/7)	98.9% (268/271)	0.011	0.132

NPV: Negative predictive value
PPV: Positive predictive value

with elevated D-dimer. However, the D-dimer level is not a statistically independent predictor for PPH in singleton pregnancy.

CONFLICT OF INTEREST: There were no conflicts of interest.

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