Effectiveness of D-dimer test for detecting deep venous thrombosis in pregnant women with threatened premature delivery and abortion

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Abstract

Background Deep vein thrombosis (DVT) in pregnant women often developed pulmonary thrombosis, which could lead to death if detection and treatment are delayed. Thus, early detection and treatment of detect DVT in pregnant women should be performed. The aim of our study was to investigate the normal range of D-dimer levels and identify the cutoff value of D-dimer to detect DVT in pregnant women with threatened premature delivery and abortion. **Methods** All singleton pregnant women hospitalized for longer than 4 days due to threatened premature delivery and abortion were identified. D-dimer levels were measured at least once per week from hospitalization to delivery. We classified pregnant women into DVT or non-DVT group. **Results** In our study, 335 pregnant women were included. A total of 3722 blood samples were obtained. There were 6 women in the DVT group and 329 in the non-DVT group. There were more women complicated with thrombophilia in the DVT group ($p < 0.01$). The means and standard deviations of D-dimer levels in the non-DVT group were 1.75 ± 0.19 $\mu\text{g/mL}$ before 28 weeks, 2.75 ± 0.1 $\mu\text{g/mL}$ from 28 to 35 weeks, and 3.22 ± 0.21 $\mu\text{g/mL}$ after 35 weeks. When the cutoff value of the D-dimer to detect DVT was set at 4.8 $\mu\text{g/mL}$, the sensitivity and specificity were 100% and 85.86%, respectively. **Conclusion** D-dimer levels of pregnant women with threatened premature delivery and abortion gradually increased as gestational age progressed. The appropriate D-dimer cut-off levels might be useful in the detection of DVT.

Background

The incidence of venous thromboembolism (VTE) in pregnant women ranges from 0.05% to 0.3% [1–3]. The risk of VTE in pregnant women increased from 4.3- to 6.7-fold compared to that in non-pregnant patients due to hypercoagulability during pregnancy [4–6]. Pregnant women with deep venous thrombosis (DVT) frequently developed pulmonary thrombosis, which could lead to death if detection and treatment are delayed [7–9]. Thus, early detection and treatment of DVT in pregnant women should be performed.

As a screening method for DVT, D-dimer assays were frequently used in non-pregnant patients because sensitivity and specificity were 88% and 59%, respectively, when the cutoff D-dimer value was set at 0.5 $\mu\text{g/mL}$ [10,11]. However, this method could not be applied to pregnant women because their D-dimer level increased gradually as the gestational age progressed despite the absence of DVT [12–14]. Actually, the mean and standard deviation (SD) of D-dimer levels in singleton pregnant women were 0.81 ± 0.82 $\mu\text{g/mL}$ at the first trimester, 1.61 ± 1.45 $\mu\text{g/mL}$ at the second trimester, and 2.37 ± 2.22 $\mu\text{g/mL}$ at the third trimester [12]. Therefore, if the screening test was performed for pregnant women when the cutoff D-dimer value was set at 0.5 $\mu\text{g/mL}$, most pregnant women are subjected to an additional test, which did not make much sense.

In contrast, the following risk factors of VTE were reported: previous VTE, obesity and immobility due to prolonged sitting, malignancy, hormone replacement therapy, pregnancy, and bed rest >3 days [15]. One of the most common pregnancy complications was threatened premature delivery. Once women

developed threatened delivery and abortion, they were forced to submit to long-stay hospitalization and prolonged immobility [16]. Therefore, because women with threatened premature delivery had at least two risks of VTE, the development of a diagnostic method for VTE is needed.

Herein, the aim of our study was to examine the trend of D-dimer during hospitalization and establish the appropriate cutoff value of D-dimer to detect VTE in pregnant women with threatened premature delivery and abortion.

Methods

Singleton pregnant women admitted to our hospital for threatened premature delivery and abortion for more than 4 days from 2010 to 2018 were identified. Because most pregnant women with threatened premature delivery and abortion for less than 3 days delivered within 3 days from hospitalization for any reason and did not undergo D-dimer test, they were excluded. The pregnant women underwent D-dimer level test at least once a week. The criterion of performing lower limb vein ultrasonography for diagnosis of DVT was D-dimer level elevation of one and half times more than previous D-dimer levels or development of leg pain, edema, or Homans sign. The women were classified into two groups: pregnant women with DVT (DVT group) and those without DVT (non-DVT group). D-dimer levels were measured using the latex agglutination turbidimetry using the CS-2100i, Sysmex Company, Kobe, Japan. The normal range of D-dimer levels is from 0.0 µg/mL to 0.9 µg/mL at our institution. Clinical information was obtained through the medical records. Thrombophilia was defined as Thrombophilia was defined as protein S or C decline to normal lower limit or presence of anticardiolipin antibody or lupus anticoagulant. The test of thrombophilia was not routinely done for all patients and performed according to the decision of clinicians. The several parts were examined with compression and power doppler ultrasonography. The lack of compressibility and the detection of slow venous flow were diagnosed with DVT.

Statistical analysis was performed using JMP Pro 13.1.0 statistical software package. Data are presented as means ± SD. Differences between the means were tested by analysis of variance and Tukey-Kramer honest significant difference test between each group, and categorical variables were compared using the χ^2 test, Fisher's exact test, or linear regression analysis by least-squares method. The D-dimer cutoff value for the detection of DVT was determined using the receiver operating characteristic (ROC) curve. At that time, the maximum D-dimer value of each pregnant woman throughout the entire pregnancy period was used. A P-value <0.05 was considered statistically significant.

Results

During the study period, 335 pregnant women were included in our study. A total of 3722 blood samples were obtained. The mean number in measuring the D-dimer levels was 11 ± 7.2 per pregnant woman. There were six (1.7%) women in the DVT group and 329 (98.3%) in the non-DVT group. The characteristics of all pregnant women are shown in Table 1. Moreover, there were more pregnant women with thrombophilia in the DVT group ($p < 0.01$). There were no statistical differences in other factors

between both groups. Among three pregnant women with thrombophilia, one patient was complicated with protein S deficiency and presence of anticardiolipin antibody and lupus anticoagulant, one with protein C deficiency, and one with protein S deficiency.

The mean D-dimer levels gradually increased as the prenatal period progressed (Fig. 1). The means and SD of D-dimer levels were 1.76 ± 0.14 $\mu\text{g/mL}$ before 28 weeks, 2.78 ± 0.05 $\mu\text{g/mL}$ from 28 to 35 weeks, and 3.27 ± 0.10 $\mu\text{g/mL}$ after 35 weeks (Fig. 2). There were significant statistical differences between the mean D-dimer levels before 28 weeks, 28–35 weeks, and after 35 weeks ($p < 0.001$). Fig. 3 presents the mean, 5th percentile, and 95th percentile of D-dimer levels in the non-DVT group. Furthermore, D-dimer levels in the DVT group were plotted with the diagnosis of DVT. Fig. 4 shows the combined ROC curve of DVT and D-dimer level. The area under the curve was 0.871. When the cutoff value of D-dimer was set at 4.8 $\mu\text{g/mL}$, the sensitivity and specificity was 100% and 85%, respectively (Table 2). Additionally, with the D-dimer cutoff value at the 95th percentile, the sensitivity and specificity were 100% and 80%, respectively. The change D-dimer levels of 6 pregnant women was shown in Fig. 5.

Discussion

In our study, the D-dimer levels of singleton pregnant women who were hospitalized for more than 4 days before delivery due to threatened premature delivery and abortion had gradually increased with advancing gestational age. Six (1.7%) of 335 women developed DVT. When the cutoff value of D-dimer was set at 4.8 $\mu\text{g/mL}$, this test resulted in high sensitivity (100%) and specificity (85%).

Although previous reports had reported the frequency of VTE in pregnant women ranged from 0.05% to 0.3% [1–3], our study showed the incidence was 1.7%, which was higher than those in previous reports. This was because only pregnant women complicated with threatened premature delivery and abortion were included in our study. They had at least two DVT risk factors of not only pregnancy but also prolonged immobility induced by threatened premature delivery and abortion among several DVT risk factors. Thus, the development of DVT might be strongly associated with threatened premature delivery and abortion.

Generally, it was well known that D-dimer levels were affected by pregnancy despite the absence of DVT [12–14,17]. In fact, D-dimer levels of singleton pregnant women in the outpatient clinic were observed to increase with advancing gestational age [12]. Similarly, our study demonstrated that D-dimer levels of pregnant women with threatened premature delivery and abortion in the hospital gradually increased and that D-dimer levels in most pregnant women throughout the pregnancy period exceeded the cutoff values of D-dimer assays frequently used to detect DVT in non-pregnant patients (0.5 $\mu\text{g/mL}$) [10,11]. Therefore, the new cutoff value should be set if the D-dimer test was used as the screening method to detect DVT. Then, we analyzed the combined ROC curve of DVT and D-dimer level, and the cutoff value of D-dimer was set at 4.8 $\mu\text{g/mL}$. When the cutoff value of D-dimer was set over the 95th percentile, the sensitivity was 100%, but the specificity was lower. Thus, this cutoff value would rather be set at 4.8 $\mu\text{g/mL}$ than over the 95th percentile because of a similar sensitivity but higher specificity. Also, Chan WS et al

demonstrated D-dimer testing may be useful for the diagnosis of DVT in pregnant women, combined with pretest probability assessment associated with VTE [18]. Therefore, if appropriate cut-off value of D-dimer could be set according to several clinical settings, D-dimer might be useful for pregnant women as the screening method.

Furthermore, 3 of 6 (50%) pregnant women with DVT had thrombophilia. Previous reports showed pregnant women with thrombophilia develop DVT more frequently than do those without thrombophilia [19,20]. However, it was difficult to detect thrombophilia in all pregnant women unless they had a medical history associated with thrombosis. Several guidelines such as those of the American College of Obstetricians and Gynecologists and Royal College of Obstetricians and Gynaecologists did not mention thrombophilia screening as a routine test [21,22]. Because DVT could induce lethal situation, further study should examine whether thrombophilia screening was effective for pregnant women for long-term hospitalization.

The limitation of our study was that this was a single-institutional and retrospective analysis. Moreover, because DVT was a rare complication during pregnancy, there were very few pregnant women with DVT in our study. However, our study demonstrated the possibility that D-dimer was useful in detection of DVT in pregnant women.

Our study showed that D-dimer levels of singleton pregnant women hospitalized for threatened premature delivery and abortion gradually increased as the gestational ages progressed. Further larger prospective studies should examine the most appropriate cutoff value of D-dimer to detect DVT.

List Of Abbreviations

VTE: Venous thromboembolism

DVT: Deep venous thrombosis

ROC: Receiver operating characteristic

Declarations

Disclosure of potential conflicts of interest

None.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki

and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. For the retrospective analysis, informed consent was not obtained. This study was approved by the Clinical Research Ethics Committee of the National Defense Medical College.

Consent to publication

All data was anonymised so individual consent for publication was not applicable.

Availability of data and materials

All data analysed in this study are available from the corresponding author upon reasonable request.

Competing interests

All authors declare that they have no competing interests.

Fundings

None.

Author Contributions

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Tables

Table 1. Characteristics of all pregnant women in our study

	DVT group (n=6)	non-DVT group (n=329)	<i>p</i> -value
Age (mean±SD*)	33±2	32±0.3	0.76
Days from hospitalization to delivery (mean± SD)	55±11	38±1	0.054
Body mass index (kg/m ²) (mean±SD)	23±6	21±4	0.50
Parity			
Primipara	3 (50%)	148 (45%)	0.99
Multipara	3 (50%)	181 (55%)	
Placenta previa complication			
Yes	0 (0%)	11 (3%)	0.99
No	6 (100%)	318 (97%)	
Hypertensive disorders during pregnancy			
Yes	0 (0%)	10 (3%)	0.99
No	6 (100%)	319 (97%)	
Smoking			
Yes	0 (0%)	12 (4%)	0.99
No	6 (100%)	317 (96%)	
Thrombophilia**			
Yes	3 (50%)	0 (0%)	<0.01
No	3 (50%)	329 (100%)	

*SD, standard deviation

**Thrombophilia is defined as protein S or C deficiency and presence of anticardiolipin antibody and lupus anticoagulant.

Table 2. Sensitivity and specificity of detection of deep vein thrombosis using D-dimer level

	D-dimer cutoff value	
	95th percentile*	4.8 µg/mL
Sensitivity	100%	100%
Specificity	80%	85%
Positive predictive value	1%	1%
Negative predictive value	100%	100%

*95th percentile of D-dimer levels according to gestational week in pregnant women without deep venous thrombosis.

Figures

Figure 1

Distribution of D-dimer levels in pregnant women without deep venous thrombosis according to gestational age. The mean D-dimer levels at each gestational week were used as the data for the study subjects

Figure 2

Box plot of D-dimer levels in pregnant women without deep venous thrombosis. We calculated the median D-dimer level per gestational week for each pregnant woman and divided them into 3 groups (before 28 weeks, 28–35 weeks, and after 35 weeks). The means $\pm$ SDs of D-dimer levels were 1.76 ± 0.14 $\mu\text{g/mL}$ (before 28 weeks), 2.78 ± 0.05 $\mu\text{g/mL}$ (28–35 weeks), and 3.27 ± 0.10 $\mu\text{g/mL}$ (after 35 weeks), and there were significant differences between each parameter before 28 weeks, at 28–35 weeks, and after 35 weeks (each $p\text{-value} < 0.001$; Fig. 2)

Figure 3

Changes in D-dimer levels of the reference group according to gestational week and D-dimer levels of the deep vein thrombosis (DVT) group at diagnosis. Points 1–5 indicate the D-dimer levels of the women complicated with DVT at diagnosis. We obtained the median D-dimer level per gestational week of each women and plotted the mean, 5th percentile, and 95th percentile of the median value per gestational week

Figure 4

Receiver operating characteristic curve of D-dimer level predicting deep venous thrombosis (DVT)

Figure 5

Changes in D-dimer levels of 6 pregnant women with vein thrombosis (DVT) group.