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The Predictive Value of D-Dimer Test for Venous Thromboembolism During Puerperium: A Prospective Cohort Study

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Abstract

The aim of this study was to investigate the D-dimer for prediction of venous thromboembolism (VTE) events in puerperium and to identify other risk factors associated with the occurrence of VTE. This was a prospective observational cohort study, which included 16 127 women who gave birth after 28 weeks of gestation at Women's Hospital of Zhejiang University, School of Medicine, from January 2016 to December 2016. Data including basic maternal and fetal characteristics, pregnancy complications, and predictive biomarkers within postpartum 24 hours including D-dimer, platelet, and fibrinogen were collected for analyses. In the cohort study, 19 (0.12%) women were identified as VTE, including 1 pulmonary embolism event and 18 deep venous thrombosis events. The receiver operating characteristic curve analysis suggested the best cutoff point for D-dimer level within postpartum 24 hours was 3.695 mg/L, with a specificity of 75.5% and a sensitivity of 73.7%, and there was no statistical correlation between fibrinogen and VTE, as well as between platelets and VTE. On multivariate analysis, age $\geq$35 years (odds ratio [OR] = 2.895, 95% confidence interval [CI]: 1.079-7.773), scarred uterus (OR = 3.894, 95% CI: 1.234-12.282), intrauterine infection (OR = 7.214, 95% CI: 1.519-34.262), antiphospholipid syndrome (OR = 199.530, 95% CI: 15.152-2627.529), D-dimer $\geq$3.70 mg/L (OR = 7.573, 95% CI: 2.699-21.247), and emergency cesarean delivery (OR = 23.357, 95% CI: 2.819-193.508) were independently associated with VTE in puerperium. We concluded that D-dimer $\geq$3.70 mg/L was an independent predictor of VTE during puerperium and D-dimer testing was necessary for perinatal women.

Keywords

D-dimer, venous thromboembolism, puerperium, risk factors

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Introduction

Venous thromboembolism (VTE) includes pulmonary embolism (PE) and deep venous thrombosis (DVT), which is 1.0 to 1.8/1000 in women during pregnancy and puerperium.[1] The incidence is 4 to 5 times higher among pregnant and postpartum women than that of nonpregnant women.[2] Pregnancy-related VTE has gradually become one of the leading causes of maternal mortality,[3] taking the place of postpartum hemorrhage, which has been highly prevented and treated.

In China, as a consequence of the adjustment of the birth policy and the changes in lifestyle and fertility concept, the maternal age is increasing and the incidence of complications in pregnancy is increasing. Many risk factors have been linked to VTE, such as thrombophilia, cesarean delivery, and obesity,[4,5] which were more likely to occur in older mothers. However, there is a lack of a suitable indicator for predicting VTE. There are some VTE risk assessment models for pregnancy, such as the VTE Risk Assessment Scale provided by the guideline from Royal College of Obstetricians and Gynaecologists.[6] But most of the scoring systems have not yet been

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validated in a large sample of prospective studies in the obstetric population.

Previous studies have shown that in nonpregnant individuals, D-dimer testing is used for the diagnosis of acute VTE with high sensitivity, moderate specificity, and high negative predictive value and is a reliable screening tool for eliminating VTE.[7] However, for pregnant women, D-dimer concentration increased progressively during the pregnancy and peaked at the first postpartum day.[8] Most healthy pregnant women have higher D-dimer values during pregnancy and puerperium than the normal reference range.[9] A prospective study showed that in the first trimester, 84% women had normal D-dimer, in the second trimester 33%, and in the third trimester only 1%, which suggests that D-dimer has no practical diagnostic use of VTE if the threshold for abnormal is used.[10]

Although the role of D-dimer testing in the investigation of pregnant-related VTE remains controversial, actually, it is still being used by clinicians. If the D-dimer level was abnormally high, the need for prophylactic use of low-molecular-weight heparin (LMWH) was decided by the doctors according to their own experiences. Therefore, we designed a prospective observational analysis to identify the incidence and risk factors of VTE during the postpartum period. Furthermore, we investigated the predictive value of coagulation markers, specifically D-dimer, platelet, and fibrinogen, and attempted to determine a suitable threshold for the assessment in the postpartum period.

Methods

Patients

The study was initiated in January 2016, and we prospectively collected the data of all women who gave birth after 28 weeks of gestation at Women's Hospital of Zhejiang University, School of Medicine, until December 2016. Women with incomplete clinical data or with VTE disease before delivery were excluded from this study (Figure 1). We set $\alpha = 0.05$ and $\beta = 0.10$ (power = 0.90), the sample size of this study was larger than the estimated sample size according to the reported incidence of pregnancy-related VTE. All clinical variables were recorded, including age, body mass index (BMI), gestational weeks of delivery, pregnancy times, parity, number of births, fetal position, mode of delivery, postpartum hemorrhage, fetal birth weight, pregnancy complications, and predictive biomarkers with postpartum 24 hours including D-dimer, platelet, and fibrinogen. All biomarker values were obtained from the same laboratory affiliated to the hospital.

Clinical Diagnosis of VTE

Diagnostic criteria for VTE: Imaging evidence as a diagnostic criterion for thrombosis or embolism. Deep venous thrombosis was diagnosed by upper and lower extremity venous color Doppler ultrasound and/or computed tomographic (CT) venography, and PE was diagnosed by CT pulmonary angiography.

Imaging examinations were required if the following conditions were present (1) with main complaint of swelling of the limbs, pain, or tenderness during movement of the limbs, measurement of inconsistencies in the thickness of the limbs on both sides, or symptoms of dyspnea, chest pain, and so on; (2) with multiple high-risk factors or the risk of VTE was considered higher by the clinician after evaluation. When imaging examination indicated the diagnosis of VTE, anticoagulation and antithrombotic therapy would be started immediately. All of the VTE patients were instructed to follow-up in the vascular department after discharge. Other women were followed up in the communities and would be accessed by vascular specialist in case of suspicious VTE symptoms.

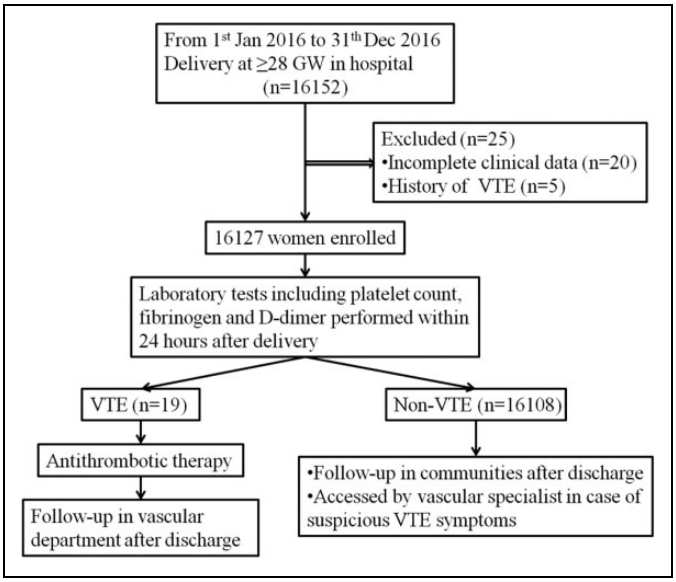

Figure 1. Flow chart of indicating the women excluded from and included in the study.

Laboratory Assays

Laboratory tests, including platelet count, fibrinogen, and D-dimer were performed. The detection of platelet count was measured by impedance (XN9000; Sysmex, Kobe, Japan). The detection of fibrinogen was measured by the solidification (Stago-R, Paris, France). The detection of D-dimer was measured by the latex-enhanced immunoturbidimetry (Stago-R, Paris, France) (normal reference range for nonpregnant adults is less than 0.5 mg/L).

Based on receiver operating characteristic (ROC) curve analysis, the best cutoff point for D-dimer level within postpartum 24 hours was 3.695 mg/L (Figure 2). For convenience in clinical practice, the predefined cutoff value for dichotomized variables of D-dimer was set at 3.70 mg/L.

Statistical Analyses

Continuous variables were described as means $\pm$ standard deviation. Student t test was used to compare the difference in the continuous variables. Chi square test, Yate's correction of continuity, or Fisher exact test was used to compare the

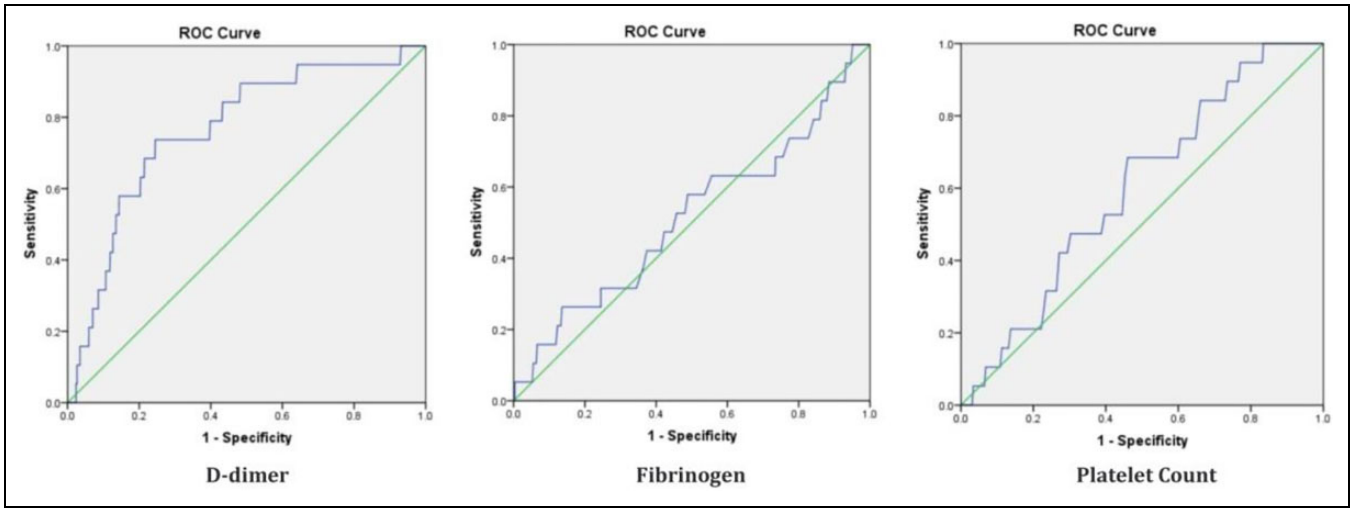

Figure 2. Receiver operating characteristic curve for D-dimer, fibrinogen, and platelet count within postpartum 24 hours. AUC (ROC of D-dimer): 0.765 ($P < .001$); AUC (ROC of fibrinogen): 0.516 ($P = .810$); AUC (ROC of platelet count): 0.599 ($P = .136$). AUC indicates area under the curve; ROC, receiver operating characteristic.

difference in the categorical variables. The forward stepwise multiple logistic regression is performed in the variables that had a univariate association with VTE ($P < .05$) to estimate the risk factors of VTE. The ROC curves of D-dimer, fibrinogen, and platelet count within postpartum 24 hours were also analyzed. The statistical analyses were performed using SPSS version 22.0 (IBM Corporation, New York, New York). Statistical significance was set at $P < .05$.

Results

Completed clinical data were available for 16 127 women (Figure 1). Eleven patients used aspirin or prophylactic/therapeutic dose of LMWH because of antiphospholipid syndrome or thrombophilia. In the cohort study, 19 (0.12%) women were identified as VTE, including 1 PE event and 18 DVT events. The DVT events included 1 woman suffering from bilateral internal iliac vein embolization, 3 women with bilateral DVT of lower extremity, 5 women with DVT of right lower extremity, and 9 with DVT of left lower extremity. Venous thromboembolism occurred at a median of 4 days postpartum (range: 2-11 days).

The D-dimer test results of all VTE women exceeded the upper limit of the reference value (0.5 mg/L). The ROC curve analysis suggested the best cutoff point for D-dimer level within postpartum 24 hours was 3.695 mg/L, with a specificity of 75.5% and a sensitivity of 73.7%. When the cutoff value was set at 5.50 mg/L, the specificity could increase to 85.5%, but the sensitivity would decrease to 57.9%; when the cutoff value was set at 7.10 mg/L, the specificity could increase to 90.0%, but the sensitivity would decrease to 31.6%. The areas under the curve of fibrinogen and platelets were close to 0.5, indicating that there was no statistical correlation between them and VTE (Figure 2).

Table 1 shows a comparison of general characteristics between VTE women and non-VTE women. Heights, neonatal weight, gestational weeks of delivery, fibrinogen, and platelet count were not significantly associated with VTE. The average age of VTE women was significantly higher than that of non-VTE women (34.05 vs 30.83 mg/L, $P = .001$). The average D-dimer within postpartum 24 hours in VTE women was significantly higher than that of non-VTE women (6.38 vs 3.44 mg/L, $P < .001$).

The risk factors predisposing to VTE in puerperium were analyzed in Table 2. Mode of delivery, age $\geq$35 years, scarred uterus, relative cephalopelvic disproportion, intrauterine infection, postpartum hemorrhage, antiphospholipid syndrome, and D-dimer $\geq$3.70 mg/L were significantly associated with VTE in puerperium (Table 2).

A multivariate model using forward stepwise regression was constructed to identify the risk factors associated with VTE in puerperium. Age $\geq$35 years, scarred uterus, intrauterine infection, antiphospholipid syndrome, D-dimer $\geq$3.70 mg/L, and emergency cesarean delivery were independently associated with VTE in puerperium (Table 3).

Discussion

The rate of VTE during puerperium in this study was 0.12%, which was consistent with previously published data.[1,11] Most cases of DVT events in our study occurred in the left lower extremity, which was related to the more serious venous stasis of the left lower extremity caused by the compression of the pregnant uterus.[12] It was considered that the use of aspirin or LMWH may affect the incidence of VTE and the results of D-dimer testing, but it does not affect the relationship between D-dimer and VTE. In fact, only 11 patients used aspirin or heparin in this study, which had little impact on the incidence

Table 1. Comparison of General Characteristics Between VTE and Non-VTE Women (x ± SD).

	VTE (n = 19)	Non-VTE (n = 16 108)	*t* Value	*P* Value
Age (years)	34.05 ± 4.59	30.83 ± 4.23	3.314	.001
Height (cm)	161.11 ± 5.76	160.50 ± 4.66	0.563	.573
BMI before pregnancy	22.19 ± 2.13	21.07 ± 2.67	1.841	.066
BMI before delivery	27.20 ± 2.52	26.43 ± 3.04	1.106	.269
Gain weight during pregnancy (kg)	12.95 ± 2.78	13.80 ± 4.30	−0.868	.386
Neonatal birth weight (g)	2987.90 ± 533.75	3215.12 ± 579.03	−1.710	.087
Gestational age at delivery (weeks)	37.53 ± 1.47	38.30 ± 2.29	−1.469	.142
D-dimer within postpartum 24 hours (mg/L)	6.38 ± 4.32	3.34 ± 3.49	3.809	<.001
Fibrinogen within postpartum 24 hours (g/L)	4.57 ± 0.91	4.65 ± 0.80	−0.449	.653
Platelet within postpartum 24 hours (10^9/L)	171.47 ± 36.81	191.62 ± 56.35	−1.558	.119

Abbreviations: BMI, body mass index; VTE, venous thromboembolism; x ± SD, mean ± standard deviation.

Table 2. Risk Factors Predisposing to VTE in Puerperium.

Risk Factors	VTE (%), n = 19	Non-VTE (%), n = 16 108	χ^2 Value	*P* Value
Previous obstetric history				
0	10 (52.63)	9166 (56.90)	0.141	.707
≥1	9 (47.37)	6942 (43.10)		
Parity				
1	17 (89.47)	15546 (96.51)	1.090	.296
≥2	2 (10.53)	562 (3.49)		
Fetal position of singleton cases				
Head	14 (82.35)	14785 (95.10)		.051[a]
Breech	3 (17.65)	647 (4.16)		
Transverse	0 (0.00)	114 (0.73)		
Mode of delivery				
Vaginal delivery	1 (5.26)	8528 (52.94)		<.001
Emergency cesarean delivery	9 (47.37)	1710 (10.62)	32.828	
Elective caesarean section	9 (47.37)	5870 (36.44)		
Age ≥35 years	10 (52.63)	3173 (19.70)	10.997	<.001
In vitro fertilization (IVF)	2 (10.53)	527 (3.27)		.127[a]
Scarred uterus	11 (57.89)	3784 (23.49)	10.644	.001
Relative cephalopelvic disproportion	1 (5.26)	317 (1.97)		.315[a]
Placenta previa	2 (10.53)	465 (2.89)		.104[a]
Adherent placenta	3 (15.79)	765 (4.75)		.059[a]
Fetal growth restriction	1 (5.26)	125 (0.78)		.139[a]
Premature birth	4 (21.05)	1852 (11.50)	0.892	.345
Macrosomia (birthweight ≥4000 g)	0 (0.00)	914 (5.67)	0.328	.567
Premature rupture of membranes	5 (26.32)	3535 (21.95)	0.033	.855
Fetal distress	3 (15.79)	3001 (18.63)	<0.001	.982
Intrauterine infection	2 (10.53)	181 (1.12)		.019[a]
Postpartum hemorrhage	3 (15.79)	688 (4.27)		.046[a]
Anemia	6 (31.58)	4530 (28.12)	0.112	.738
Intrahepatic cholestasis of pregnancy	2 (10.53)	479 (2.97)		.109[a]
Gestational diabetes mellitus	3 (15.79)	2437 (15.13)	0.058	.810
Hypertensive disorders of pregnancy	3 (15.79)	883 (5.48)	2.152	.142
Cardiac insufficiency	1 (5.26)	30 (0.19)		.036[a]
Uterine rupture	1 (5.26)	65 (0.40)		.075[a]
Antiphospholipid syndrome	1 (5.26)	7 (0.04)		.009[a]
D-dimer ≥3.70 mg/L	14 (73.68)	3947 (24.50)	22.190	<.001
D-dimer ≥5.50 mg/L	11 (57.89)	2341 (14.53)		<.001
D-dimer ≥7.10 mg/L	6 (31.58)	1607 (9.98)		<.001

Abbreviation: VTE, venous thromboembolism.
[a]Evaluated by Fisher exact test.

Table 3. Multivariate Logistic Regression of VTE Risk Factors During Puerperium.

Risk Factors	*P* Value	Odds Ratio	95% Confidence Interval
Age ≥35 years	.035	2.895	1.079-7.773
Scarred uterus	.020	3.894	1.234-12.282
Intrauterine infection	.013	7.214	1.519-34.262
Antiphospholipid syndrome	<.001	199.530	15.152-2627.529
D-dimer ≥3.70 mg/L	<.001	7.573	2.699-21.247
Emergency cesarean delivery	.003	23.357	2.819-193.508

Abbreviation: VTE, venous thromboembolism events.

of VTE and the results of D-dimer testing, thus we did not exclude these 11 patients from the study.

Good predictive biomarkers may help with early prevention to reduce the morbidity and mortality of VTE. In this study, we found that fibrinogen and platelet count had little correlation with VTE. However, there was a certain correlation between the D-dimer level within postpartum 24 hours and VTE. There are many advantages to using D-dimer in the diagnosis of pregnancy-related VTE, such as noninvasive, quick, does not harm the fetus, may reduce the need for imaging, and is inexpensive compared to other methods of diagnosis. Although collected data showed that D-dimer levels of 2 groups were universally elevated beyond the standard threshold of 0.5 mg/L, the average D-dimer level in VTE group was significantly higher than that in non-VTE group. Although the specificity and sensitivity of the cutoff value of 3.695 mg/L were not so high, the predictive value of D-dimer test for VTE in puerperium was confirmed. The multivariate analyses also showed that D-dimer ≥3.70 mg/L was independently associated with VTE in puerperium. Before that, guidelines from Royal College of Obstetricians and Gynaecologists recommended that D-dimer testing should not be performed in the investigation of acute VTE in pregnancy.[13] Guidelines from American College of Obstetricians and Gynecologists recommended that the rise of D-dimer cannot predict VTE reliably.[14] However, our study suggested D-dimer ≥3.70 mg/L as a risk factor of VTE in puerperium. If the D-dimer is more than 3.70 mg/L, other VTE-related risk factors should be carefully evaluated. We recommend the use of LMWH to prevent VTE when the lever of D-dimer is more than 5.50 mg/L and the use of imaging examination to screen for VTE when the lever of D-dimer is more than 7.10 mg/L.

In recent years, there were also some studies trying to find a new D-dimer reference range or cutoff value for the diagnosis of pregnancy-related VTE, but the results were diverse for different laboratories, assays, and instruments. A prospective study involving 89 women advised D-dimer test with the new threshold for the first trimester of 286 ng/mL, the second trimester of 457 ng/mL, and the third trimester of 644 ng/mL can be useful in the diagnosis of pregnancy-related VTE.[10] Parilla et al investigated 61 women and concluded that a combination of D-dimer levels along with a modified Wells score can be used in pregnancy to triage women into a low-risk category for PE.[15] A cross-sectional study involved 760 pregnant women suggesting a gestation-specific reference range for D-dimer concentrations (approximately week 6 to week 42) and recommended using the 95th centile potential cutoff values as diagnosis basis of VTE in pregnancy.[16] A meta-analysis involved 30 studies proposed that D-dimer levels reached a peak at 48 to 72 hours postpartum with a mean value of 6.44 mg/L.[17] There were still no universal hemostatic reference ranges during pregnancy and postpartum. Each laboratory testing D-dimer concentrations should determine its own recommended normal cutoff value. Moreover, most studies did not directly clarify the diagnostic value of D-dimer for VTE. Hunt et al calculated that the AUC for D-dimer in pregnant and puerperal women was 0.668 and concluded no diagnostically useful threshold for diagnosing or ruling out VTE.[18] In our study, the ROC curve analysis showed that D-dimer has statistical correlation with VTE and suggested the best cutoff point for D-dimer level within postpartum 24 hours was 3.695 mg/L. Furthermore, we originally proposed that D-dimer ≥3.70 mg/L is an independent predictor of VTE during puerperium, which confirmed the predictive value of D-dimer for VTE during puerperium.

Although no cases of D-dimer-negative VTE in puerperium were found in our study, we didn't recommend that normal D-dimer levels can exclude pregnant-related VTE, for case report had described the occurrence of acute VTE in pregnant women with negative d-dimer level.[19] A retrospective study of pregnant women with suspected PE who had both V/Q scans and D-dimer testing found a negative likelihood ratio of 1.8, suggesting that a negative D-dimer is inadequate to exclude PE in pregnancy.[20] Other risk factors should also be taken into consideration when estimating the likelihood of a delivered woman's VTE.

Our study revealed several independent risk factors of VTE in puerperium, including age ≥35 years, scarred uterus, intrauterine infection, antiphospholipid syndrome, and emergency cesarean delivery. These factors have been confirmed in similar studies, although risk factors observed differentiated between these studies.[4,5,6,11,21] A meta-analysis found that the risk of VTE was 4-fold greater following cesarean delivery than following vaginal delivery and was greater following emergency cesarean delivery than following elective cesarean delivery.[6] A population-based controlled cohort study involved 634 292 delivered women showed that higher BMI, older age, thrombophilia, multiple pregnancy, cesarean delivery, gestational diabetes, threatening premature birth, anemia, chorioamnionitis, in vitro fertilization with ovarian hyperstimulation, primiparity, and cardiac diseases were associated with postpartum VTE events.[11] Another population-based cohort study showed that increased age was associated with VTE during postpartum.[21] It also reported postpartum hemorrhage to be a risk factor for postpartum VTE, while our study found that postpartum hemorrhage was associated with VTE, but not an independent risk factor for VTE.

The limitation of this study is that the number of VTE cases is insufficient, but this is consistent with the incidence of pregnancy-related VTE. Other limitations of this study included the effects of choice bias, for all the women in this

study were at our hospital, and loss to follow-up bias, for we could hardly get the data of follow-up in communities and vascular department. Furthermore, this study did not discuss the predictive effect of D-dimer test for VTE during pregnancy and 24 hours after postpartum, which need further study.

Conclusion

In summary, we demonstrated that D-dimer $\geq$3.70 mg /L was independently associated with VTE in puerperium. The predictive value of D-dimer test for VTE in puerperium was confirmed. Other independent risk factors of VTE in puerperium were older age, scarred uterus, intrauterine infection, antiphospholipid syndrome, and emergency cesarean delivery. We believe our study provides new evidence, which will aid the ability of clinicians to judge whether the women are at a high risk of VTE in puerperium.

Authors' Note

Wen Hu and Yali Wang contributed equally to this work. This article was approved by Medical Ethics Committee of Women's Hospital, Zhejiang University School of Medicine. Informed consent was not obtained because no patient information was published herein.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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