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Research Article

# Deep vein thrombosis in early pregnancy: A retrospective study

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ABSTRACT

*Objective:* To investigate the clinical characteristics, management, and prognosis of deep vein thrombosis (DVT) during early pregnancy.
*Methods:* We conducted a retrospective study among women with DVT during their first trimester of pregnancy who were admitted to the obstetrics department of Peking University People's Hospital between March 2008 and May 2021.We analyzed clinical data of eight patients, including their general condition, obstetric characteristics, diagnosis, treatment, and gestational outcomes.
*Results:* Risk factors for DVT in the first trimester included personal history of DVT, thrombophilia and immune diseases, and DVT was more likely to affect the left leg. The main manifestation of DVT was pain or swelling of the affected limbs. D-dimer levels after anticoagulant treatment showed a downward trend compared with those before treatment ($P = 0.09$), while D-dimer levels increased significantly after delivery compared with those before delivery ($P = 0.03$). All the patients started on low-molecular-weight heparin (LMWH) therapy after a diagnosis of DVT. Temporary inferior vena cava (IVC) filters were implanted in 3 patients with mixed thrombosis before delivery, but were removed after the operation. Except for 1 case with thrombophilia who refused treatment, others underwent anticoagulation therapy from 6 weeks to 1 year postpartum. Seven patients achieved a successful delivery with live births.
*Conclusion:* During early pregnancy, DVT was more common in women with maternal risk factors. More cases of venous thromboembolism (VTE) were observed in the left leg. For women with a high risk of DVT, medical intervention, early identification, accurate diagnosis and precise treatment during early pregnancy should be promoted.

## 1. Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of mortality and obstetric morbidity. It is currently believed that PE and DVT are different manifestations and stages of the same disease in different parts of the body. As reported, 75%–80% of pregnancy-related VTE are caused by DVT, and 20%–25% are caused by PE.[1] Women are at high risk of VTE during pregnancy and puerperium than their non-pregnant peers due to factors, including hypercoagulability, venous stasis, and vascular damage during labor.[2] Moreover, the risk of VTE increases gradually during the course of pregnancy, reaching a peak at 2 weeks postpartum.[3] There is a general consensus that VTE is less likely to happen in early pregnancy than in the puerperium.[4] More studies have been done about VTE in late pregnancy and puerperium. Herein, we aim to retrospectively analyze clinical data of patients in early pregnancy with DVT in their lower extremities and were treated at the Obstetrics Department of Peking University People's Hospital in the last 13 years. This will improve the understanding of the clinical information and management of DVT in early pregnancy.

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## 2. Materials and methods

### 2.1. Study participants

We collected the clinical data of 8 patients who were diagnosed with DVT in early pregnancy and admitted for labor in the Obstetrics Department of Peking University People's Hospital from March 2008 to May 2021. Information, including age, body mass index (BMI), gravidity and parity history, chief complaints of DVT, gestational week, location of DVT diagnosis, medical and surgical comorbidities, obstetric complications, gestational week at childbirth, delivery methods, labor complications, and gestational outcomes were retrospectively analyzed for all patients.

The Royal College of Obstetricians and Gynecologists (RCOG) scoring system was used to assess the risk of VTE in all the patients before delivery and during the puerperium.[5] The patients were divided into low-risk (0–2 points), intermediate-risk (3 points) and high-risk groups (≥4 points).[2]

### 2.2. Diagnosis of DVT

Combined with the high-risk factors, main complaints, and symptoms and signs of the patients, a diagnosis of DVT was confirmed by color Doppler ultrasound. DVT cases were divided into 3 patterns: (1) central thrombosis manifesting as thrombogenesis in the common iliac, external and internal iliac, and common femoral veins; (2) peripheral thrombosis characterized by thrombi in the venous plexus of the calf muscle below the popliteal vein; and (3) mixed thrombosis referred to as peripheral venous thrombi, extending upward and involving the entire deep venous system of the lower extremities.[6]

### 2.3. Laboratory tests

Routine screening for lupus-related antibodies, anti-cardiolipin antibodies, anti-β2-glycoprotein, proteins C and S, and antithrombin activity was performed to determine whether the patients had immune diseases and thrombophilia. We analyzed and compared the values of routine blood tests [red blood cell count (RBC), hematocrit (HCT), hemoglobin (HB) and platelet count (PLT)] and coagulation function tests [prothrombin time (PT), activated partial thromboplastin time (APTT), prothrombin international normalized ratio (INR), fibrinogen (Fib) and serum D-dimer] before and after anticoagulant treatment for the first time, and before and after childbirth.

### 2.4. Treatment of DVT

All the patients were administered standard prophylaxis or therapeutic anticoagulation regimens of low molecular weight heparin (LMWH) when diagnosed with DVT in early pregnancy. Individualized therapy plans were formulated according to different conditions. During the treatment period, coagulation function was regularly checked, and color Doppler ultrasound was performed to monitor thrombi fluctuation. Anticoagulation treatment ended when the thrombi disappeared.

### 2.5. Statistical methods

Statistical analyses were performed using SPSS.20 statistical software. General and obstetric characteristics of the patients were descriptively analyzed. Quantitative data are expressed as mean ± standard deviation (SD) if normally distributed. A paired sample *t*-test was used for comparisons between the 2 groups. Non-normally distributed quantitative data were expressed as median values (minimum-maximum), and the Wilcoxon signed-rank test was used when the 2 groups were compared. Qualitative data were expressed in terms of the number of patients and percentages. A $p$ value of $<0.05$ indicates statistically significant difference.

## 3. Results

### 3.1. General and obstetric characteristics

The average age of the 8 patients in this study was 30.8 ± 3.8 years. Only one case (12.5%) was over 35 years old. Table 1 shows the patients' clinical characteristics. One case (12.5%) was overweight [BMI≥ 25 (kg/$m^2$)], and 2 cases (25%) were underweight [BMI< 18.5 (kg/$m^2$)] before pregnancy. Six women (75%) were primiparous, and the others were multiparous. Two cases (25%) had personal history of DVT; one case (12.5%) had a history of long-term use of contraceptives. Seven of the 8 patients (87.5%) had pregnancy comorbidities. Two cases (25.0%) had immune diseases, of which one case (12.5%) was diagnosed as acute systemic lupus erythematosus (SLE) with secondary antiphospholipid antibody syndrome (APS). One case (12.5%) was found to have thrombophilia during pregnancy. Seven patients (87.5%) were natural pregnant, and one patient (12.5%) was conceived by assisted reproductive technology/in vitro fertilization (ART/IVF). The occurrence time of DVT was from 7 weeks to 12 weeks of gestation. All the patients survived until the last follow-up visit.

### 3.2. Assessment of high-risk factors for VTE

The average risk score of VTE before labor was 3.00 ± 2.39 with 4 patients (50%) in the low-risk group, one patient (12.5%) in the medium-risk group and 3 patients (37.5%) in the high-risk group. The average risk score after labor was 3.25 ± 2.44. Moreover, the number and proportion of cases in different risk groups after labor were the same as those before labor. As shown in Table 1, the risk factors for DVT in early pregnancy mainly included personal history of VTE (2/8), low-risk and high-risk thrombophilia (2/8), age (1/8), ART/IVF (1/8), family history of VTE (1/8), acute SLE (1/8) and multiple pregnancies (1/8).

### 3.3. Symptoms and signs

Our patients mainly complained of pain (7/8, 87.5 %) or swelling (3/8, 37.5 %) in the affected legs. One case (12.5 %) caught fever. One case (12.5 %) had no obvious clinical manifestations; however, she was diagnosed with DVT after she underwent color Doppler ultrasonography due to elevated D-dimer levels (Table 1).

### 3.4. Diagnosis

All the patients were diagnosed using color Doppler ultrasonography. Eight patients with DVT were documented in total, with 6 left-sided DVT, 1 right-sided DVT, and 1 bilateral DVT. As shown in Table 1, the pattern of thrombosis was mainly mixed thrombosis (5/8, 62.5%), followed by peripheral thrombosis (3/8, 37.5 %).

### 3.5. Laboratory findings

#### 3.5.1. Blood routine tests

There was no statistical difference when comparing RBC, HCT, HB and PLT values before and after anticoagulation treatment for the first time and, before and after labor ($p > 0.05$) (Tables 2 and 3).

#### 3.5.2. Coagulation function tests

There was no obvious change when comparing PT, APTT, INR, fibrinogen, and D-dimer values before and after the anticoagulation treatment for the first time ($p> 0.05$), and post-treatment D-dime values in post-treatment showed a significant downward trend compared to pre-treatment values [581(283–3807)ng/mL vs 948(230–5690)ng/mL, $p = 0.09$]. Comparison showed no considerable difference in the PT, APTT, INR and fibrinogen values between the antenatal and postpartum groups ($p > 0.05$); however, the D-dimer levels increased significantly after labor [747 (465–1101) vs 1924 (594–5418) ng/mL, $p = 0.03$] (Tables 2 and 3).

**Table 1**
Demographic and clinical features of women with DVT in early pregnancy (n = 8).

| No | Age (years) | Pre-pregnant BMI (kg/m^2) | Gravida/Parity | Past medical history & complications | Comorbidities | ART/IVF | Risk factors | Immunoantibodies positive | Gestational weeks with DVT | Chief complaints |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 31 | 23.30 | 2/1 | Personal DVT history, scarred uterus (after myomectomy) | Uterine fibroids, mild anemia | Yes | Personal DVT history after surgery | No | 11 | Pain |
| 2 | 34 | 18.83 | 3/2 | None | Underweight, mild anemia | No | None | No | 7 | Elevated D-dimer |
| 3 | 32 | 21.45 | 2/2 | Preeclampsia during last pregnancy | APS, thrombocytopenia | No | Preeclampsia history | Yes | 10 | Swelling, pain |
| 4 | 30 | 17.99 | 2/1 | Placental abruption, scarred uterus (after CS) | SLE, secondary APS | No | Placental abruption history | Yes | 12 | Pain, fever |
| 5 | 25 | 16.56 | 1/1 | Bilateral tonsillectomy, right breast fibroma resection | Underweight, mild anemia | No | None | No | 10 | Swelling, pain |
| 6 | 37 | 25.22 | 3/1 | Personal DVT history, scarred uterus (after myomectomy) | Overweight, uterine fibroids (red degeneration) | No | Personal DVT history in the puerperium | / | 10 | Pain |
| 7 | 30 | 21.78 | 1/1 | Long-term use of contraceptives | None | No | Hormone use History, embryo arrest of one of the twins | / | 9 | Pain |
| 8 | 27 | 22.77 | 1/1 | None | Thrombophilia | No | Thrombophilia, family DVT history | No | 9 | Swelling, pain |

| No | Location of DVT | Treatment Modality | Mode of delivery | Gestational weeks of delivery (weeks) | Outcomes | Labor complications | Antenatal VTE risk score | Postnatal VTE risk score |
|---|---|---|---|---|---|---|---|---|
| 1 | Left soleus vein | Thromboprophylaxis with LMWH from onset to 6 weeks postpartum | CS | $38^{+3}$ | Full-term live birth | None | 5 | 5 |
| 2 | Left soleus vein | Thromboprophylaxis with LMWH from onset to 6 weeks postpartum | VD | 31 | Preterm live births, mild neonatal asphyxia | Postpartum hemorrhage, placenta bipartita, placenta abruption | 0 | 1 |
| 3 | Left common iliac vein, external iliac vein, common femoral vein, superficial femoral vein, deep femoral vein, great saphenous vein | Therapeutic anticoagulation with LMWH from onset to 4 days postpartum, IVC filter implantation before CS, warfarin from the first day after implantation to one year postpartum, IVC filter removal at half a month postpartum | CS | $37^{+5}$ | Full-term live birth | None | 2 | 2 |
| 4 | Left common iliac vein, external iliac vein, superficial femoral vein, deep femoral vein, great saphenous vein, inguinal vein | Therapeutic anticoagulation with LMWH from onset to 2 weeks postpartum, then oral rivaroxaban to half a year postpartum | Medical abortion | $13^{+3}$ | Miscarriage | None | 3 | 3 |
| 5 | Left common femoral vein, deep femoral vein, superficial femoral vein, great saphenous vein, popliteal vein, anterior tibial vein, posterior tibial vein, peroneal vein; right common femoral vein, deep femoral vein, superficial femoral vein, great saphenous vein | Therapeutic anticoagulation with LMWH from onset to 4 months postpartum, IVC filter implantation before CS, IVC filter removal at half and three months postpartum | CS | 38 | Full-term live birth | Oligohydramnios | 1 | 1 |
| 6 | Left femoral vein, superficial femoral vein, popliteal vein, peroneal vein | Thromboprophylaxis with LMWH from onset to 1 weeks antepartum, change to therapeutic anticoagulation with LMWH due to elevated D-dimer | VD | $28^{+3}$ | Preterm live births, severe neonatal asphyxia, very low birth weight infants | Umbilical cord prolapse, foot presentation | 6 | 7 |
| 7 | Left common femoral vein, deep femoral and superficial femoral veins, | Therapeutic anticoagulation with LMWH from onset to 9 days postpartum, IVC filter implantation at one week before VD, IVC filter | VD | 39 | Full-term live birth | None | 1 | 1 |

(*continued on next page*)

**Table 1** (*continued*)

| No | Location of DVT | Treatment Modality | Mode of delivery | Gestational weeks of delivery (weeks) | Outcomes | Labor complications | Antenatal VTE risk score | Postnatal VTE risk score |
|---|---|---|---|---|---|---|---|---|
| | popliteal vein, posterior tibial vein, peroneal vein | removal at one month postpartum, warfarin from 4 days to half a year postpartum | | | | | | |
| 8 | Right peroneal vein | Therapeutic anticoagulation with LMWH from onset to one month later, change to prophylatic dose with LMWH from negative ultrasound result to one day antepartum, refusal to anticoagulation treatment after labor | CS | $39^{+1}$ | Full-term live birth | None | 6 | 6 |

DVT: deep vein thrombosis; VTE: venous thromboembolism; BMI: Body Mass Index; ART/IVF: assisted reproductive technology/in vitro fertilization; APS: anti-phospholipid antibody syndrome; SLE: systemic lupus erythematosus; IVC: inferior vena cava; CS, cesarean section; VD, vaginal delivery; LMWH, low molecular weight heparin;/, not applicable.

**Table 2**
Comparison of the laboratory findings before and after anticoagulant treatment.

| Laboratory indicators | Pre-treatment (n = 8) | Post-treatment (n = 8) | *p*-Value |
|---|---|---|---|
| RBC(10^9/L) | 9.24 ± 1.57 | 8.55 ± 2.49 | .43 |
| HCT(%) | 34.37 ± 4.10 | 33.33 ± 4.00 | .51 |
| HB(g/L) | 116.83 ± 12.43 | 111.67 ± 13.20 | .30 |
| PLT(10^9/L) | 201.83 ± 41.59 | 225.00 ± 37.57 | .16 |
| PT(s) | 12.03 ± 1.17 | 11.51 ± 1.10 | .10 |
| APTT(s) | 28.15 (24.70–28.80) | 27.85 (25.30–38.10) | .26 |
| Fib(mg/dl) | 411.70 ± 157.69 | 429.11 ± 113.35 | .66 |
| INR | 1.07 ± 0.08 | 1.03 ± 0.09 | .16 |
| D-dimer(ng/ml) | 948 (230–5690) | 581 (283–3807) | .09 |

RBC: red blood cell count; HCT: hematocrit; HB: hemoglobin; PLT: platelet count; PT: prothrombin time; APTT: activated partial thromboplastin time; Fib: fibrinogen; INR: prothrombin international normalized ratio.

**Table 3**
Comparison of the laboratory findings before and after childbirth.

| Laboratory indicators | Prepartum (n = 8) | Postpartum (n = 8) | *p*-Value |
|---|---|---|---|
| RBC(10^9/L) | 9.08 ± 2.50 | 11.67 ± 3.72 | .10 |
| HCT(%) | 34.08 ± 7.92 | 33.78 ± 3.64 | .70 |
| HB(g/L) | 116.81 ± 10.72 | 114.13 ± 13.00 | .46 |
| PLT(10^9/L) | 222.29 ± 91.28 | 175.38 ± 97.45 | .24 |
| PT(s) | 10.63 ± 0.54 | 11.07 ± 0.82 | .14 |
| APTT(s) | 28.86 ± 3.34 | 30.24 ± 2.58 | .27 |
| Fib(mg/dl) | 437.29 ± 50.27 | 404.71 ± 63.05 | .14 |
| INR | 0.95 ± 0.05 | 0.98 ± 0.07 | .18 |
| D-dimer(ng/ml) | 747 (465–1101) | 1924 (594–5418) | .03* |

RBC: red blood cell count; HCT: hematocrit; HB: hemoglobin; PLT: platelet count; PT: prothrombin time; APTT: activated partial thromboplastin time; Fib: fibrinogen; INR: prothrombin international normalized ratio.

### 3.6. Treatment

All the patients received prophylactic or therapeutic anticoagulation treatment with LMWH from the onset. Among the 5 patients with mixed DVT, 3 were placed on retrievable inferior vena cava (IVC) filters, which filters were removed at about half a month to three and half a month if no residual thrombus was discovered. Except for 1 patient who refused anticoagulation therapy, the other patients continued treatment until 6 weeks to 1 year postpartum. In detail, 4 patients used LMWH till 6 weeks to 4 months postpartum. Two patients switched to warfarin after 4–6 days of superimposition with LMWH, and the dosage of warfarin according to their INR value. One case used rivaroxaban for half a year (Table 1).

### 3.7. Gestational outcomes

All the patients are still alive till date. After the DVT diagnosis in early pregnancy, 1 patient (12.5%) was subsequently found to have acute SLE and secondary APS, and her pregnancy was terminated by medical abortion. The other patients achieved successful delivery, including 4 patients (50.0 %) via cesarean section and 3 patients (37.5%) via vaginal delivery. All the newborns were alive, of which 2 were preterm births, and suffered from neonatal asphyxia. One patient experienced premature abruption of the placenta and postpartum hemorrhage.

## 4. Discussion

### 4.1. Risk factors and thromboprophylaxis

Nearly 2000–3000 babies are delivered every year in the Obstetrics Department of Peking University People's Hospital. According to the 2020 Queensland clinical guidelines, VTE complicates approximately 1.2 of every 1000 births, and the risk of VTE is higher in the third trimester than in the first and second trimesters.[7] Consequently, it is estimated that VTE occurred in 30–50 pregnant women in our center in the last 13 years. Epidemiological data showed that the median incidence rates of VTE were 1, 1.4, and approximately 3 per 10,000 pregnant women in the first, second, and third trimesters, respectively. Approximately 20% of antepartum VTEs occur in the first trimester, 20% in the second trimester, and 50% in the third trimester.[8] In this study, 8 patients with VTE in early pregnancy were retrospectively analyzed, which is consistent with the incidence reported in the literature. In other words, VTE is relatively uncommon in early pregnancy. After analyzing 575 pregnant women with VTE from 9 hospitals in China, Wang et al. found that patients with a personal history of VTE had a higher incidence of recurrent VTE in early pregnancy, and 23.1% of those who had no high-risk factors suffered VTE during early pregnancy.[2] The first 3 risk factors for VTE during early pregnancy were age ≥35 years, assisted conception, and staying on bed to prevent miscarriage ≥3 days.[4] In this study, the main risk factors for VTE in early pregnancy were personal history of VTE, low-risk or high-risk thrombophilia, immune diseases, and family history of VTE. A personal history of VTE is the primary risk factor for VTE recurrence and pregnancy increases the risk of recurrence by 3-to 4-folds. Inherited and acquired thrombophilia are also risk factors for VTE.[3,8,9] Additionally, deficiency of protein C, protein S, and antithrombin III increases the risk of VTE, and a family history of VTE increases this risk. It is worth noting that even in the absence of thrombophilia, a family history of VTE can increase the risk of VTE by 4-folds.[3] Acquired thrombophilia is largely caused by APS.[3,9] In our study, 2 cases had a personal history of VTE; 2 cases had immune diseases (1 case of APS, 1 case of acute SLE and secondary APS); 1 case had thrombophilia (proteins C and S were lower than

normal) and family history of VTE. Compared with Western populations, acquired thrombophilia and internal diseases, rather than inherited thrombophilia are more prevalent in Chinese populations.[4] Therefore, we may need to focus on screening for maternal factors and pay attention to pregnant women with a personal or family history of VTE, thrombophilia and immune diseases.

Modalities used for VTE prevention include mechanical and pharmacological prophylaxis for VTE are LMWHs. LMWHs are the agents of choice for thromboprophylaxis. Standard or high prophylactic doses of LMWHs were generally used along with therapeutic doses for some pregnant women with extreme risk factors. There is no consensus on the thromboprophylaxis for VTE in early pregnancy, and differences remain in the different guidelines. The 2015 RCOG guidelines recommend hierarchical thromboprophylaxis management if the antenatal VTE score is $\geq$ 4and prophylactic measures should be considered from the first trimester.[5] LMWH standard prophylaxis after assessment is suggested by the 2020 Queensland clinical guidelines under the same circumstance.[7] In our cases, two patients had a personal history of DVT after surgery and in the puerperium, respectively. Patients received therapeutic anticoagulation with LMWH after being diagnosed with DVT in the first trimester. However, prophylactic doses of LMWH should be administered before the diagnosis of DVT because they have risk factors according to the guidelines.[5,7] We need to combine the actual situation and different guidelines, accumulate evidence-based medical data, and promote VTE risk assessment.

### 4.2. Assessment and diagnosis

Because the symptoms and signs of pregnancy-related VTE are similar to the physiological changes during pregnancy, diagnosing of VTE presents more challenges.[10] Therefore, we should document case histories, conduct physical examinations, and further imaging tests. Our data showed that DVT in early pregnancy was more likely to be mixed and peripheral with complaints of pain or swelling in the affected extremity, which is consistent with the literatures.[6,10,11] Interestingly, DVT tended to affect the left leg, probably due to the effect of the gravid uterus and right common iliac artery compressing the left common iliac vein, which is called the May-Thurner-like syndrome.[10,11]

Color Doppler ultrasonography is the first-choice investigation for the diagnosis of DVT because it has high sensitivity and accuracy and is universally used in clinical practice.[11] For pregnant women with suspected DVT and negative color Doppler ultrasound results, magnetic resonance venography without the use of contrast agents can be an option.[6] In this study, color Doppler ultrasonography was used for the diagnosis and follow-up of pregnant women with DVT in early pregnancy. We found that the main types of thrombi were mixed and peripheral, which is in agreement with the literature. Compared to non-pregnant women, VTE in pregnant women is more likely to occur in the proximal veins.[3,10]

However, there is a lack of effective laboratory examinations for VTE during pregnancy. As a degradation product of fibrin complex, D-dimer is a sensitive indicator that reflects the body's hypercoagulable state, and it is a valuable index for the diagnosis of acute VTE in non-pregnancy situations. Acute VTE can be safely ruled out by negative D-dimer levels. Nevertheless, D-dimer levels increase with gestational age in pregnant women whose blood gradually becomes hypercoagulable, peaking on the first day after delivery. Consequently, the non-pregnancy threshold (500 ng/mL) for D-dimer may not be suitable for pregnant women.[12] Our study confirmed that D-dimer levels in pregnant women with DVT at early pregnancy increased during pregnancy and after labor and decreased after anticoagulation treatment. This suggests that D-dimer tests may assist in disease surveillance and efficacy assessment, although the use of D-dimer alone is limited. Due to the deficiency of a suitable D-dimer for healthy pregnant women, a comprehensive analysis should consist of symptoms, signs, and color Doppler ultrasound results. Yan et al. reported that the decrease in RBC, HB, and HCT during pregnancy may have early predictive value for the diagnosis of VTE.[13] However, the study found no significant difference in RBC, HB, HCT, and PLT values before and after anticoagulation treatment or childbirth and values of the above indexes were within the reference ranges for healthy individuals.

### 4.3. Current management approaches

#### 4.3.1. Supportive care

Patients with proximal DVT should get out of bed as soon as possible after adequate anticoagulation treatment considering thrombus shedding and disease aggravation, and patients with distal DVT should get out of bed as early as possible.

#### 4.3.2. Anticoagulant therapy

Anticoagulant treatment is instrumental in reducing preexisting and new thrombi. Unfractionated heparin and LMWH are the most evidence-based drugs for the treatment of pregnancy-related VTE.[3,10] Most guidelines recommend LMWH as the first-line treatment for acute VTE in pregnant women,[10] unless there are contraindications such as thrombocytopenia ($<75 \times 10^9$/L) and active bleeding.[5] In this study, 1 patient had thrombocytopenia with platelet count over $90 \times 10^9$/L; however, no bleeding occurred during the anticoagulant treatment. For patients with VTE during pregnancy, anticoagulants should be administered until 6 weeks postpartum, preferably up to 3 months postpartum since the first 2weeks after delivery is the peak period of VTE occurrence.[3,5,7] Majority of the cases in this study continued anticoagulation treatment until 6 weeks to 1 year postpartum, when the thrombus disappeared, as shown by the color Doppler ultrasound.

Low-dose aspirin is not recommended for thromboprophylaxis during pregnancy.[5,7] Warfarin, the most commonly used vitamin K antagonist, can pass through the placenta and have teratogenic effects on the fetus; thus, it is not safe for pregnant women, except when the patients are equipped with mechanical heart valves. However, warfarin can be used during breastfeeding. When the risk of bleeding is reduced, anticoagulants can be changed from LMWH to warfarin after delivery, and INR levels need to be monitored during warfarin use. Oral thrombin and factor Xa inhibitors are also not recommended for pregnant and lactating women.[5,7] Since breastfeeding is not a problem of concern in our study, 1 patient underwent an induced abortion using rivaroxaban for half a year after labor.

#### 4.3.3. Thrombolytic therapy

Thrombolytic therapy, including catheter-directed thrombolysis (CDT) and systemic thrombolysis during pregnancy, is controversial and lacks relevant research data. In spite the fact that there are some reports of full-term pregnancy and successful childbirth after treatment, CDT is not a routine recommended treatment method and it should be avoided, especially during the first trimester. However, CDT can be used as an alternative when the body is threatened or the drugs fail during the second and third trimesters.[3] Studies have shown that the survival rate of pregnant women receiving systemic thrombolytic therapy was as high as 94%, but there was a 28.4% risk of postpartum hemorrhage. Nevertheless, the fetal or neonatal mortality rate related to systemic thrombolytic therapy is 12%, and 35.1% of pregnant women experienced premature delivery.[14] It is assumed that fetal death may be associated with hemodynamic changes caused by thrombosis and thrombolytic drugs.

#### 4.3.4. Inferior vena cava filters

The IVC filters are mainly used to reduce the occurrence of fatal PE. The indications of IVC filters for DVT in pregnant women are the same as those for non-pregnant women.[6] As the guidelines point out, IVC filter implantation is suggested when there are contraindications for anticoagulation therapy or some complications, or PE still occurs despite adequate anticoagulation therapy. The specific application indications are as follows: (1) floating thrombus in the iliac vein, femoral vein or inferior vena cava; (2) CDT, percutaneous mechanical thrombectomy

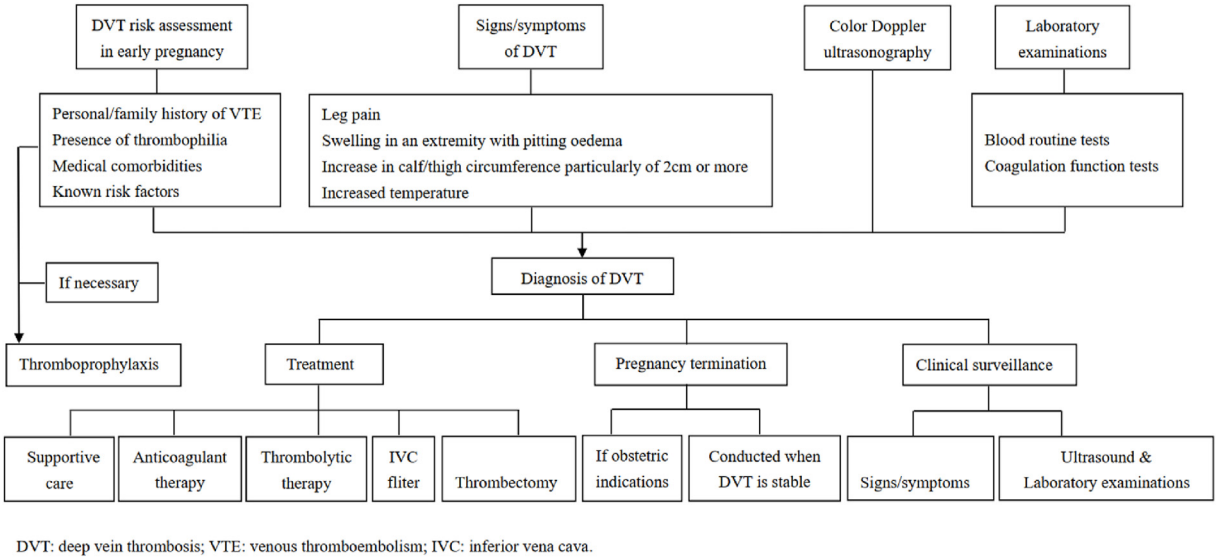


**Fig. 1.** Flow chart showing DVT assessment, diagnosis and management for women in early pregnancy.

(PMT) or thrombectomy for acute DVT; and (3) abdominal, pelvic, or lower extremity surgery with high-risk factors for acute DVT and PE. Patients with DVT during early pregnancy should avoid IVC filter implantation due to the impact of X-rays on the fetus. Patients with high-risk factors can be implanted with IVC filters before delivery in case of sudden changes in abdominal pressure and possible thrombus shedding during labor.[6] In this study, 4 cases with mixed thrombosis achieved successful delivery. The IVC filters were placed in cases before vaginal delivery or cesarean section to avoid the PE based on the first application indication mentioned above. The filters were removed after the condition was stable after childbirth.

#### *4.3.5. Thrombectomy*

Thrombectomy is an effective method that removes blood clots and can quickly relieve venous obstruction. When thrombosis is extensively formed in the lower extremities and there is a risk of PE, surgical thrombus removal is an option.[15] Thrombectomy can have a good outcome, but it depends on the professional knowledge of the surgeon and whether there is an extracorporeal circulation device.[3]

### *4.4. Pregnancy termination and prognosis*

Currently, there is no conclusion regarding whether to terminate pregnancy with DVT. It is generally believed that if appropriate diagnosis and treatment methods are achieved, there will be no definite adverse effects on the mothers and newborns. Termination of pregnancy is not recommended if DVT is stable, but only when there are obstetric indications.[16] As suggested, termination of pregnancy should be conducted according to the gestational weeks when the patient is in a stable condition.[16] In our study, the pregnancy of a patient with acute SLE and secondary APS was terminated at about 13th week of gestation after her immune diseases were stabilized. Overall, most patients with DVT in their first trimester had good gestational outcomes.

Due to the relatively low incidence of VTE during early pregnancy, few cases were included in the study. This is a limitation of our study and more samples are needed in future work. A larger multicenter longitudinal study from early pregnancy-late pregnancy-puerperium is necessary to validate the relationship of high-risk factors and occurrence of DVT in the future.

## 5. Conclusion

The risk of DVT of the lower extremities during early pregnancy should not be overlooked. Our study summarized the flow chart of DVT assessment, diagnosis, and management in women in early pregnancy in Fig. 1. We suggest that all pregnant women should undergo a risk assessment for VTE using a standardized risk assessment tool. Maternal factors, such as a personal history of DVT, immune diseases and thrombophilia should be screened, and appropriate prophylaxis or treatment regimens should be selected based on the actual situation to prevent complications and improve outcomes.

## Ethical considerations

This study was approved by the Institutional Ethics Committee of Peking University People's Hospital.

## Consent to participate

Written informed consents were obtained from all the participants involved in the study.

## Author contributions

ZC: acquisition and analysis of clinical data, manuscript writing; ZXM: final approval; LGL: conceptualization, data validation and final approval.

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## Declaration of competing interest

None.

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