Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2023**; 50(6): 128
https://doi.org/10.31083/j.ceog5006128

Original Research

Clinical Analysis of 6 Cases of Lower Extremity Venous Thrombosis in Early Pregnancy

Danni Xiong[1], Xiaoshuang Pang[1], Jie Duan[2,*]

[1]Department of medical college, Wuhan University of Science and Technology, 430081 Wuhan, Hubei, China
[2]Department of Gynecology, Hubei Maternal and Child Health Hospital, 430070 Wuhan, Hubei, China
*Correspondence: xiaojie192021@163.com (Jie Duan)
Academic Editor: Paolo Ivo Cavoretto
Submitted: 1 December 2022 Revised: 29 January 2023 Accepted: 10 February 2023 Published: 19 June 2023

Abstract

Background: This study aims to investigate the clinical features, diagnosis and treatment of deep vein thrombosis in early pregnancy. **Methods**: The clinical manifestations, diagnosis, treatment and prognosis of 6 pregnant women with deep vein thrombosis in early pregnancy who were hospitalized in Hubei Maternal and Child Health Hospital from July 2020 to July 2022 were analyzed retrospectively. **Results**: One patient underwent inferior vena cava angiography + inferior vena cava filter placement + indwelling catheter thrombolysis + lower extremity venous balloon dilatation followed by uterine curettage to terminate the pregnancy, and 3 patients underwent uterine curettage after low molecular weight heparin therapy. Thrombosis was alleviated in the remaining 2 patients who were still continuing the pregnancy. **Conclusions**: Lower extremity venous thrombosis in early pregnancy was not an indication for termination of pregnancy. A good clinical prognosis can still be obtained after early detection, diagnosis, and treatment.

Keywords: early pregnancy; lower extremity venous thrombosis; thrombophilia

1. Introduction

Venous thromboembolism (VTE) refers to the abnormal agglutination of blood in the venous lumen, which blocks the venous lumen and leads to venous return disorder. VTE includes pulmonary embolism (PE) and deep venous thrombosis (DVT). Pregnancy is one major risk factor for VTE. The risk of VTE increases approximately 5-fold and 60-fold during pregnancy and puerperium, respectively [1]. The study found that the probability of thrombosis was consistent in different gestation periods, with a slight increase in early and late pregnancies (33.3% and 31.9%, respectively) [2]. Early identification of thrombosis has a crucial impact on pregnancy outcomes. In this study, 6 cases of DVT in early pregnancy were retrospectively analyzed in order to provide reference for the diagnosis and treatment of DVT in early pregnancy.

2. Materials and Methods

2.1 General Data Collection

The clinical data of 6 pregnant women with DVT in early pregnancy who were admitted to our hospital from July 2020 to July 2022 were retrospectively analyzed. Inclusion criteria: clinical gestational age $<$14 weeks; Diagnosis of DVT by intravenous Doppler ultrasound: (1) There was substantial echo in venous lumen; (2) Venous vessels were not deflated; (3) Color and pulsed Doppler ultrasound showed no autonomic or irritating blood flow at the thrombus site; All patients were treated with antithrombotic therapy. Exclusion criteria: patients with lower extremity thrombosis after termination of pregnancy; Patients with thrombosis in other parts; Patients with lost clinical data. General data: age, body mass index (BMI), gestational weeks, pregnancy duration, clinical manifestations, high risk factors, and B-scan ultrasound (Table 1); Laboratory parameters: thrombophilia related testing markers, coagulation function, blood routine test and D-dimer level (Tables 2,3).

2.2 Methods

Clinical data of 6 cases were collected. SPSS 26.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis of the data. The difference between normal distribution measurement data groups was compared using independent *t* test and non-parametric test.

3. Results

3.1 General Information

A total of 6 pregnant women were enrolled in the study, ranging in age from 28 to 33 years old, with an average of (30.3 $\pm$ 2.1) years old. The minimum gestational week was 5 weeks, and the maximum gestational week was 12+ weeks, with an average of (8.6 $\pm$ 2.6) weeks. Where, 1 case (16%) underwent assisted reproduction, and 1 case (16%) was complicated with hyperemesis gravidarum. 4 cases (66%) were primipara; 2 cases (33%) were multiparas. There were 2 cases (33%) with a history of thrombosis. See Table 1 for details.

Table 1. General information of 6 patients with DVT in early pregnancy.

Case	Age	Body mass index	Gestational weeks (W)	Gravidity and parity	Clinical manifestation	Complications or high risk factors	B-ultrasound
1	32	22.58	11	P0A0	Right lower extremity pain	Hyperemesis gravidarum	Intermuscular vein thrombosis in right peroneal vein
2	31	25.7	8.4	P1A0	Right calf pain	History of left calf intermuscular venous thrombosis	Right calf intermuscular venous thrombosis
3	28	20.8	6.5	P0A0	Left lower limb swelling with numbness	Artificial embryo transfer	Left common femoral vein thrombosis
4	33	19.03	5	P0A5	Swelling of right lower limb	-	Incomplete embolization of right common femoral vein and gastrocnemius muscle tip
5	30	17.57	8.4	P1A0	Right lower limb soreness	History of left lower extremity venous thrombosis after cesarean section	Right calf intermuscular venous thrombosis
6	28	24.8	12	P0A2	Left lower extremity pain	None	Intermuscular vein thrombosis of left lower extremity

Table 2. Thrombosis-related test indicators.

Case	Protein C activity	Protein S activity	Antithrombin	DRVVT normalized ratio of Lupus anticoagulant	SCT normalized ratio of Lupus anticoagulant
1	95	30.6	-	0.99	0.95
2	47	6	-	1.10	1.07
3	81	144	106	1.26	1.01

DRVVT, diluted Russell viper venom time; SCT, silica clotting time.

Table 3. Comparison of related indicators before and after treatment.

	Before treatment	After treatment	T/Z value	*p* value
Coagulation function				
PT (S)	11.95 ± 1.32	12.80 ± 1.31	–1.09	0.300
APTT (S)	31.13 ± 3.44	30.91 ± 4.43	0.094	0.927
FIB (g/L)	3.25 ± 0.64	3.20 ± 0.63	0.137	0.894
D-dimer (ug/mL)	2.66 ± 2.97	0.54 ± 0.21	–2.402*	0.015*
Blood Routine + CRP				
WBC (10^9/L)	7.56 ± 1.36	7.95 ± 1.30	–0.52	0.617
HB (g/L)	128.50 ± 7.18	114.2 ± 7.63	3.36*	0.007*
CRP (mg/L)	2.34 ± 0.62	3.79 ± 1.48	–1.764	0.078

* Mann-Whitney U Test, $p < 0.05$; PT, prothrombin time; APTT, activated partial thromboplastin time; FIB, fibrinogen; CRP, C-reactive protein; WBC, white blood-cell; HB, hemoglobin; T/Z, value should be replaced by Z value.

3.2 Clinical Manifestations

Among the 6 patients, 2 cases (33%) had venous thrombosis in the left lower extremity and 4 cases (66%) had venous thrombosis in the right lower extremity. All six patients showed lower extremity pain, tenderness and acid distension discomfort (Table 1).

3.3 Diagnosis and Auxiliary Examination

All 6 patients were diagnosed by color Doppler ultrasonography, and the D-dimer level was increased in venous blood, with an average of (2.39 $\pm$ 2.58) ug/mL. Cases 1–3 underwent thrombosis-related examinations after admission. For case 2, the protein S activity was 6% (very low, and thrombophilia could not be ruled out), and for case 3, the diluted Russell viper venom time (DRVVT) standardized ratio of lupus anticoagulant was higher than normal, indicating the presence of lupus anticoagulants. See Table 2 for details. There were no statistical differences in coagulation function, leukocyte and C-reactive protein (CRP) before and after treatment ($p > 0.05$). There were statistical differences in D-dimer and hemoglobin (HB) before and after treatment ($p < 0.05$). See Table 3 for details.

3.4 Treatment of DVT in Early Pregnancy

All 6 patients received low molecular weight heparin (4100 IU, subcutaneous injection once every 12 h) treatment. Case 3 was subjected to B-scan ultrasonography after seven days of drug anticoagulation, and the results showed that the left common femoral vein thrombosis was larger than before, and the flow rates of the popliteal vein in the left lower limb, the anterior tibial vein and the posterior tibial vein were slow. Considering the poor drug anticoagulation, the combined scheme of posterior inferior vena cava angiography + inferior vena cava filter placement + indwelling catheter thrombolysis was adopted. The changes in coagulation function during treatment are shown in Fig. 1. Four patients (including those with thrombolytic therapy) underwent painless visual uterine evacuation after anticoagulant therapy, with less vaginal bleeding during the operation, and their conditions were improved after the operation. Two patients were discharged after anticoagulation treatment and continued the pregnancy. None of the 6 patients developed PE, as shown in Table 4.

4. Discussion

Pregnancy is an acquired independent risk factor for VTE. During normal pregnancy, elevated coagulation factors can lead to a hypercoagulable state, which reduces the risk of bleeding during pregnancy but causes thrombosis [3]. History of thromboembolic disease is the greatest risk factor for VTE in pregnancy. Patients with a history of thrombosis have a 3- to 4-fold increased risk of VTE recurrence during pregnancy, and VTE recurs in 15%~25% of all VTE patients in pregnancy [4]. Among the 6 cases in this paper, 2 cases (33%) had a history of thrombosis. Therefore, it is recommended that women with a history of thrombosis or a first-degree relative with a history of hereditary thrombosis should be evaluated for antiphospholipid syndrome and other hereditary thrombosis [5]. A large number of literatures indicate that thrombophilia is one risk factor for VTE in pregnancy [6,7]. The 2020 Queensland Guidelines consider thrombophilia as an independent high-risk factor, and point out that a high risk of thrombophilia involves any of the following circumstances: >1 laboratory index suggests thrombophilia, antiphospholipid syndrome, antithrombin deficiency, Leiden Factor V (FVL) homozygous mutation, prothrombin homozygous mutation, FVL/prothrombin mutation heterozygote, protein C deficiency, protein S deficiency [8]. In this study, case 2 hadprotein S activity of 6% and protein C activity of 47% after admission. Therefore, she was preliminarily diagnosed as thrombophilia (Table 3). Case 3 suggested high protein S, which was distinct from pre-existing cognition. According to the Chinese Guidelines for Diagnosis and Prevention of Thrombophilia (2021 Edition) [9]: the acute phase of VTE and anticoagulant medication will affect the level of anticoagulant protein, so the anticoagulant protein level test should be performed more than 2 weeks after the acute phase of thrombus, considering that the patients were all in the acute phase, so the results of anticoagulant protein level test for case 3 were only used to exclude the diagnosis. Assisted reproductive technology is also a high risk factor for thrombosis during pregnancy. Studies have shown that the prevalence of VTE is 10 times higher in patients receiving assisted reproductive therapy than in the general population [10]. A large number of literatures have shown that ovarian hyperstimulation, blood hypercoagulability, high estrogen levels, and multiple pregnancy are high risk factors for venous thrombosis after *in vitro* fertilization [11]. At the same time, during assisted reproductive technology (ART), the use of estrogen and progestin can increase the activity of various coagulation factors and reduce the level of anticoagulant protein, which will destroy the balance between coagulation and hemostasis, leading to thrombosis. The patients in case 3 was given progesterone injection, Progynova tablets, and dydrogesterone tablets to prevent miscarriage after transplantation, which increased the risk of thrombosis. More recent studies concluded that COVID-19 as a risk factor for thromboembolic complications in the pregnant population [12]. A systematic review shows that haemostatic and thromboembolic complications have been reported in 0.98 and 0.28% of pregnant women with COVID-19 infection respectively, the absolute risk of thromboembolic complications in pregnant women without COVID-19 is 0.1% [13]. Their data suggests that coagulopathy and thromboembolism are both increased in pregnancies affected by COVID-19. Other risk factors for thrombosis include maternal age (≥35 years), cesarean section, obesity, parity (4 or more), infection, etc. [14].

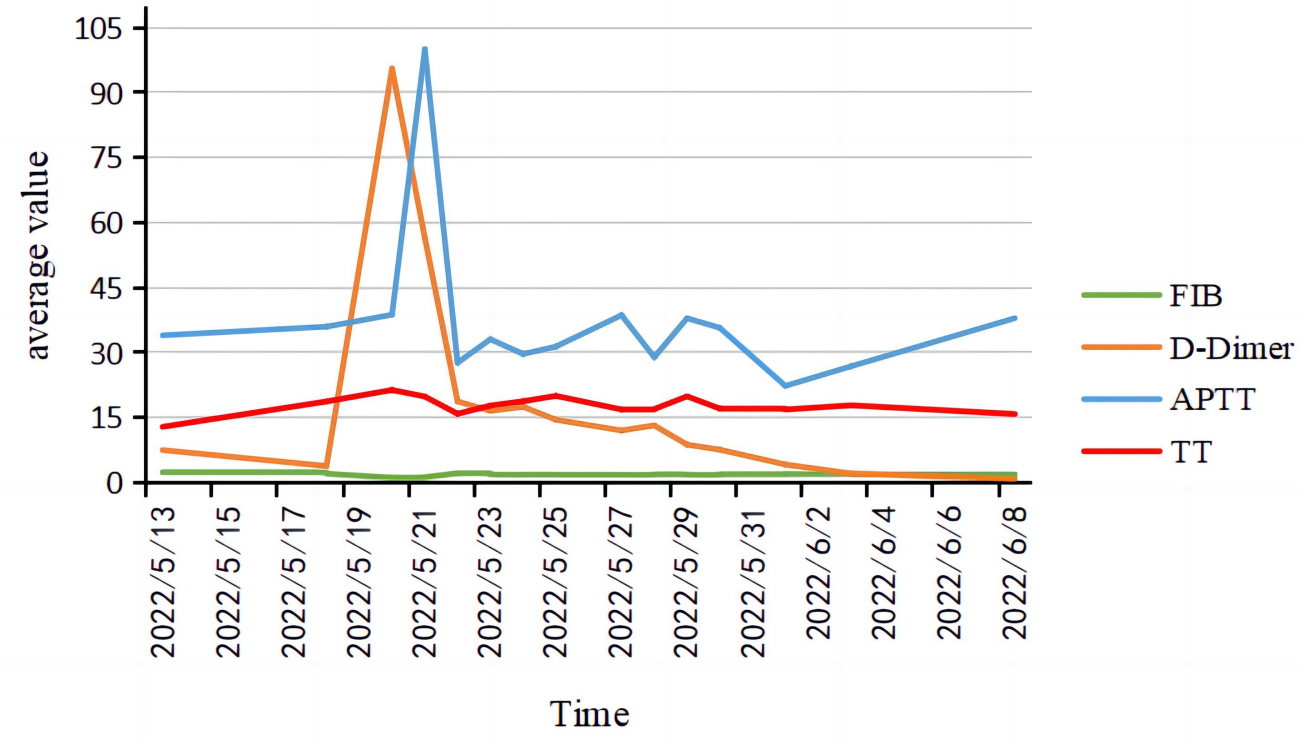

Fig. 1. Changes of coagulation function and D-dimer during treatment in case 3. 2022/5/20, Inferior vena cava angiography + inferior vena cava filter placement + indwelling catheter thrombolysis; 2022/5/30, lower extremity venous balloon dilatation + indwelling catheter extraction + lower extremity venous balloon diatation; 2022/6/1, Painless visual evacuation; 2022/6/18, Lower extremity venography + lower extremity venous filter removal. TT, thrombin time; APTT, activated partial; FIB, fibrinogen.

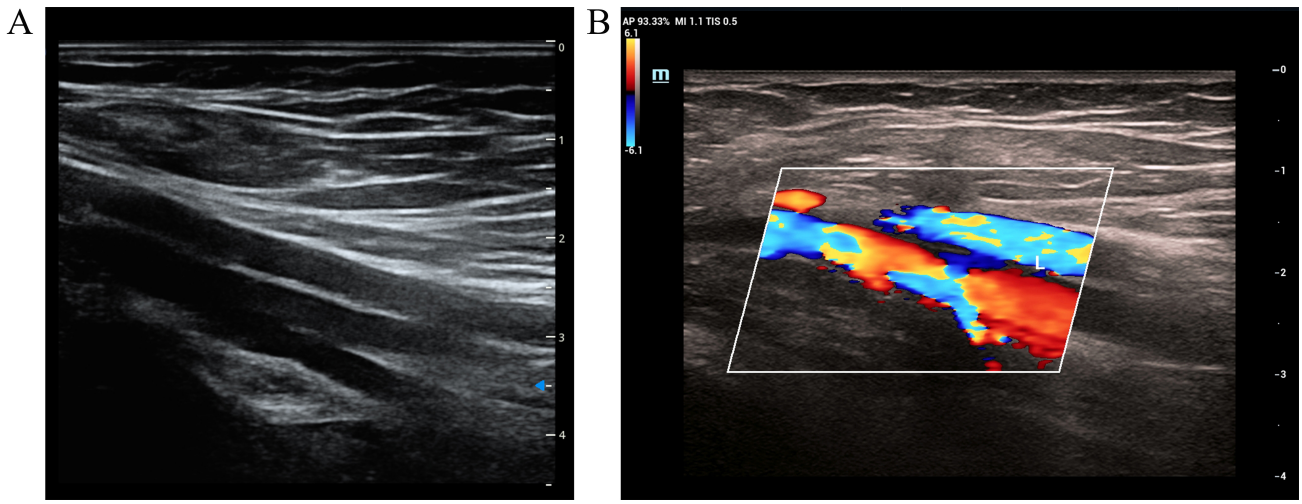

Fig. 2. B-ultrasound of lower extremity veins before and after treatment in case 3. (A) Left common femoral vein thrombus before treatment. (B) Thrombus recanalization after thrombolytic therapy.

DVT patients may be characterized by pain, swelling on one side of the limb, and cyanosis of the affected limb. Due to the difference in size of embolus, the degree of pulmonary artery obstruction varies, and there may be different degrees of dyspnea, chest pain, tachycardia and other non-specific manifestations. However, with the increase of gestational weeks in normal pregnant women, similar symptoms may appear and cover up the clinical manifestations of DVT, leading to inaccurate diagnosis of DVT and delayed treatment. In this paper, the 5 patients had different degrees of pain or swelling in the affected limbs. Compared with the swelling of the lower limbs caused by the increased uterus oppression in late pregnancy, the complaints of pregnant women in early pregnancy deserve more

Table 4. Treatment and prognosis of 6 patients with DVT in early pregnancy.

Case	Treatment process	Discharge status	Follow-up
1	enoxaparin (0.4 mL iH Q12H)	Improved and discharged, with pregnancy continued	27+ weeks of pregnancy, anticoagulation with fondaparinux sodium (0.4 mL iH QD), no obvious complications were found in regular obstetric examination
2	daltepari (0.6 mL iH Q12H)	Improved and discharged, with pregnancy continued	28+ weeks of pregnancy, no obvious lower extremity thrombosis was found in B-scan ultrasound at 20+ weeks of pregnancy. Now, low molecular weight heparin (0.4 mL iH QD) anticoagulation therapy was given. No obvious complications were found in regular obstetric examination
3	The effect of low molecular weight heparin anticoagulation is not good, and inferior vena cava angiography + inferior vena cava filter placement + indwelling catheter thrombolysis were performed. Low molecular weight heparin (0.4 mL iH Q12H) + urokinase thrombolysis was continued after surgery. After the thrombus was stabilized, lower extremity venous balloon dilatation + indwelling catheter extraction + lower extremity venous balloon dilatation were performed (Comparison of thrombus before and after treatment are shown in Fig. 2).	Improved after painless uterine curettage	Half a month later, the B-scan ultrasound of both lower extremities showed no abnormality, so inferior vena cava filter was removed, and now rivaroxaban (20 mg qd) was given for anticoagulation therapy
4	Low molecular weight heparin	Improved after painless uterine curettage	Oral administration of rivaroxaban (15 mg BID)) was given outside hospital, which was changed to 20 mg qd after 21 days. B-scan ultrasound of both lower extremities was not regularly reviewed, and there was no special discomfort
5	Low molecular weight heparin	Improved after painless uterine curettage	Oral administration of rivaroxaban (15 mg BID) was given outside hospital, which was changed to 20 mg qd after 21 days), and no abnormality was found in both lower extremities in review
6	Low molecular weight heparin	Improved after painless uterine curettage	The pregnancy was continued 5 months after the surgery. No thrombosis was found in the lower extremity B-scan ultrasound during pregnancy. Due to thrombophilia, low-molecular-weight heparin treatment was continued during pregnancy. At 39 + 4 weeks of gestation, cesarean section was performed due to a "giant child". The surgery went smoothly, with 300 mL intraoperative blood loss

DVT, deep venous thrombosis; BID, twice a day; iH, hypodermic injection; Q12H, every 12 hours; QD, once a day.

attention. Due to anatomical reasons, left-sided deep vein thrombosis has been reported in 88% pregnancies, and more than 70% pregnant women with lower extremity deep vein thrombosis are diagnosed with iliofemoral vein involvement [15]. Of the 6 cases in this paper, 4 had right lower extremity venous thrombosis and 2 had left lower extrem-

ity venous thrombosis. However, these results are not representative due to the small sample size. Pregnant women with high risk factors or high suspicion of VTE should undergo imaging examinations to confirm the diagnosis results. Dual lower extremity venous ultrasonography is the preferred examination for thrombotic diseases during pregnancy. If ultrasonography is negative, but the clinical result is highly suspected as DVT, further magnetic resonance imaging (MRI) examination should be performed to confirm the diagnosis. For pregnant women without detectable abnormality, the lower extremity venous ultrasonography can be further performed after 3~7 d to support further diagnosis. Clinically, the increase of D-dimer carries diagnostic significance for the confirmed diagnosis of VTE. In this paper, increase of D-dimer was observed in all 6 cases. However, as the level of D-dimer in pregnant women gradually increased with the progress of pregnancy, it was not recommended to use D-dimer as an indicator for the evaluation of VTE during pregnancy. If the D-dimer test result is negative, the possibility of acute pulmonary thromboembolism (PTE) during pregnancy can be completely ruled out [16]. Studies have shown that when D-dimer exceeds 0.5 mg/L, lower extremity B-scan ultrasound examination can improve the diagnostic rate of venous thrombosis [17]. The D-dimer of the six patients in this article has no statistical significance before and after treatment, which may be related to pregnancy, anticoagulation mode, small sample size, etc. The combination of D-dimer and clinical score to exclude VTE is a new direction in recent years [18], but there are few prospective studies on the relative reliability, and some of the existing findings are still controversial. Wang Xiaofeng *et al*. [19] conducted a retrospective study on 91 pregnant patients with DVT, finding that prothrombin time (PT) and activated partial thromboplastin time (APTT) were down-regulated and platelet (PLT) levels were elevated in DVT patients. The combination of the three can better predict pregnancy with lower extremity DVT than the single item, which helps early indication of pregnancy with lower extremity DVT.

Low molecular weight heparin (LMWH) is the first choice in the clinical treatment of VTE during pregnancy. LMWH in the treatment of VTE during pregnancy should be based on an individualized approach [20]. It has been pointed out that the dose of LMWH should be adjusted according to maternal body weight when formulating a treatment plan for LMWH [21]. Direct oral anticoagulants (DOACs) are small molecules that traverse the placenta and cannot be used during pregnancy or lactation, but oral DOACs during early pregnancy have not been shown to be associated with fetal malformations [8]. Studies have shown that, VTE during pregnancy should be continuously monitored for anti-Xa activity to determine the LMWH dose [22]. This method is not recommended because the measurement and precise target range remain controversial, and there are few clinical studies on the safety and efficacy of LMWH dose adjustment. Anticoagulant therapy is adequate for most cases of VTE in pregnancy. Advanced treatments such as thrombolysis, inferior vena cava filter (IVCF) and mechanical methods of thrombus removal can be associated with significant fetal morbidity and mortality and should be considered under special circumstances such as failure of other treatments, massive or sub-massive PE, or acute limb-threatening DVT. Catheter-directed thrombolysis or thrombectomy is an option for patients with limb-threatening proximal DVT [23]. Catheter directed thrombolysis theoretically has the advantages of low bleeding risk and no transplacental passage. Placement of IVCF was considered if there were contraindications to anticoagulation, no response to anticoagulant therapy, heparin induced thrombocytopenia, heparin hypersensitivity, or significant bleeding [24]. In case 3, after 1 week of anticoagulation therapy with low molecular weight heparin, B-scan ultrasound suggested a large thrombus range, so IVCF + catheter directed thrombolysis was carried out after comprehensive consideration. Intraoperatively, thrombus formation in multiple locations of the left common iliac vein, external iliac vein, and common femoral vein was observed (Fig. 2). Literature has shown that by using IVCF combined with LMWH to control the thrombus, the pregnancy can be continued. Although there is radiation during IVCF, the radiation dose will not reach the risk dose. For the sake of prenatal and postnatal care, this patient finally chose to terminate the pregnancy. At present, there is no consensus on the duration of anticoagulant therapy for maternal VTE. Relevant guidelines have recommended that the therapy should be lasted for at least 6 weeks postpartum, and the minimum duration of therapy should be 3~6 months, depending on the clinical situation [25]. For case 3, due to the abnormal coagulation function caused by catheter thrombolysis, there was bleeding at the femoral vein puncture site. Therefore, uterine curettage was performed after the thrombus was stable and the coagulation function was generally normal. In this paper, 4 cases with pregnancy termination stopped heparin therapy 24 hours before surgery After coagulation function was examined to be normal, visual uterine curettage was performed. The surgery process was smooth with little bleeding.

Guidelines have recommended that for pregnant and lying-in women without exercise contraindications, considering factors such as exercise type, intensity, and duration, moderate exercise should be performed to prevent thrombosis [26]. Mechanical methods such as graduated compression stockings (GCS) and the use of intermittent pneumatic compression devices can appropriately prevent thrombosis. Meanwhile, the new guideline also introduces the use of antithrombotic elastic socks (TED) stockings and continuous pneumatic compression devices [21]. The 2020 Queensland Clinical Guidelines also propose that patients who use anticoagulant drugs for any reason before pregnancy, have a history of VTE with a high risk of thrombophilia, recur

≥2 times of unprovoked VTE, and have VTE during pregnancy should continue prophylaxis in this pregnancy until 6 weeks postpartum. In this paper, case 6 continued pregnancy after the cure of VTE during pregnancy. Considering the history of thrombosis, she was diagnosed withf thrombophilia. Low-molecular-weight heparin anticoagulation was continued during pregnancy to prevent thrombosis until 6 weeks postpartum. It is now in the period of COVID-19 epidemic, in order to prevent thrombosis in pregnancy caused by COVID-19 infection, vaccination of pregnant women is still a priority. Women with complete or boosted vaccine doses had reduced risk for severe symptoms, complications, and death including reduced thrombotic risk [27]. For the majority of women with mild-moderate disease who are managed at home, VTE risk assessment should be performed carefully. It is emphasized in the Royal College of Obstetricians and Gynaecologist (RCOG) guidelines that LMWH should be considered for thromboprophylaxis when maternal risk factors such as immobility, high fever, and dehydration are present [28]. For those with a less severe condition and a short period of hospitalisation, 10–14 days of LMWH may be appropriate [29]. The preventive anticoagulant drugs were the same as the therapeutic drugs. At present, the preventive doses of drugs can be divided into standard preventive dose, high preventive dose and therapeutic dose. Different dose is selected according to the conditions of patients, and a unified clinical plan has not yet been formed.

5. Conclusions

To conclude, thrombotic disease during pregnancy is one important cause of maternal death, and multiple risk factors in early pregnancy can increase the risk of thrombotic disease. In the process of treating DVT in early pregnancy, both the therapeutic effect of thrombosis and the effect of treatment on the fetus should be considered. Patients requesting continued pregnancy should be actively anticoagulated during treatment until resolution of clinical symptoms and uneventful thrombus. And the patient required continuous anticoagulant therapy during pregnancy until postpartum. Patients who requested termination of pregnancy, who did not respond to anticoagulation or whose condition was worsened should be given anticoagulation therapy through thrombolysis or inferior vena cava filter first, followed by termination of the pregnancy when the thrombus control was stable and the coagulation function was normal. Patients with DVT in early pregnancy should be comprehensively evaluated for the risks of thrombus shedding, miscarriage and fetal malformation. Patients and families should carefully decide whether to continue the pregnancy to reduce long-term complications.

Availability of Data and Materials

Our datasets are included in the study.

Author Contributions

DX and JD designed the research study. DX performed the research. XP helped collect clinical data and advice. DX analyzed the data and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was approved by the Medical ethics committee of Hubei maternal and child health care hospital. Approval number: [2022]IEC[085]. The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

Acknowledgment

We would like to thank the patient, all the surgeons that involved in the treatment.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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