Venous thromboembolic disease and pregnancy

Luis J. Marfil-Rivera*

Department of Internal Medicine, University Hospital "Dr. Jose E González," Autonomous University of Nuevo Leon, Monterrey, Nuevo Leon, Mexico

Abstract

The incidence of venous thromboembolism (VTE) during pregnancy is increased by 4-50 times. It is estimated that VTE complicates between 1 and 1.5 per 1000 pregnancies. During pregnancy, hemostasis is characterized by a prothrombotic state to prevent possible bleeding during childbirth and postpartum; however, this change predisposes the mother to an increased risk of VTE. The diagnosis of VTE in pregnancy is a challenge because the clinical findings of this disease may be confused by the physiological changes of pregnancy. The treatment of VTE requires the use of anticoagulants drugs and in the pregnant patient is required a more controlled protocol. For this reason, it is important to know the physiological changes during pregnancy and the pharmacodynamics of anticoagulant drugs to prevent any hemorrhagic complications during childbirth.

Key words: Pregnancy. Venous thrombosis. Anticoagulant therapy. Blood coagulation.

Introduction

Of the possible emergencies which could occur during pregnancy, venous thromboembolism (VTE) might be the most critical; therefore, it is necessary to know the changes which develop during pregnancy and post-partum to identify those patients with a high risk of thrombosis, perform a timely diagnosis, and begin proper treatment for each case. During pregnancy, a prothrombotic stage is generated to prevent a possible hemorrhage during implantation, placentation, or delivery; however, these changes increase the risk of thrombosis^{1,3}. Pregnancy, as a risk factor for thrombosis, increases its frequency by 5-10 times compared to non-pregnant women. Its prevalence is calculated to be between 0.76 and 1.7 events per 1000 pregnancies, managing to surpass hemorrhages and hypertension as the main cause of maternal morbidity-mortality^{1,4,5}. The risk of thrombosis is uniform throughout the entire

pregnancy, yet the greater risk is during the first 6 weeks' post-partum, with 80% of events occurring in the first 3 weeks' post-partum. C-sections increase the risk of thrombosis by between 5 and 9 times compared to vaginal delivery^{1,5-7}.

VTE represents 14.9% of maternal deaths worldwide and in the western world is responsible for 10% of them (1.1 maternal deaths per 100,000 deliveries)⁸. Between 75% and 80% of cases occur as deep venous thrombosis (DVT), while between 20% and 25% are caused by pulmonary thromboembolism (PTE)⁶. Along with acute episodes, there is an additional risk of venous insufficiency; 80% of women with DVT develop post-thrombotic syndrome, and up to 60% of patients develop venous insufficiency at 5 years of follow-up⁹. Estimations suggest that at least half the cases who develop DVT or a PTE during pregnancy suffer from subacute thrombophilia. Hence, a complete knowledge of coagulation

Correspondence:

*Luis Javier Marfil-Rivera
E-mail: lmarfil@icloud.com

Date of reception: 18-12-2018
Date of acceptance: 12-04-2019
DOI: 10.24875/RMU.19000043

Available online: 27-05-2019
Medicina Universitaria. 2019;21(1):29-33
www.medicinauniversitaria.org

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Table 1. VTE risk factors

Main criteria	Secondary criteria
Prolonged immobilization (absolute rest for more than 4 days' pre-partum) Post-C-section hemorrhage with losses over 1000 mL Blood transfusion History of VTE: – Recurrent condition – During pregnancy – Caused by oral contraceptives Pre-eclampsia Diagnosis of thrombophilia – Deficiency of antithrombin III – Factor V Leiden mutation – G20210A prothrombin mutation Previous diagnosis of: – Systemic erythematosus lupus – Antiphospholipid syndrome – Cardiopathy (rheumatic, valvular, and auricular fibrillation) – Sickle cell anemia Post-partum infection	BMI over 30 kg/m ² Multiple pregnancies Multiparity Age > 35 years Post-partum hemorrhage over 1 L Consumption of over 10 cigarettes/day Thrombophilia: – C protein deficit – S protein deficit Pre-eclampsia

systems is essential, as well as of fibrinolysis and its inhibitors in relation to pregnancy^{2,3}. Diagnosis of thromboembolic events during pregnancy represents a challenge since clinical data are often masked by the physiological changes typical of gestation. There are several guidelines to identify risk factors linked to venous thromboembolic disease during pregnancy. In the following table, there is a classification which separates risk factors by the level of importance (Table 1).

Physiological changes which occur during pregnancy create a hypercoagulable state secondary to the increase of plasmatic factors II, VII, VIII, IX, X, and XII and an increase in the synthesis of fibrinogen. S protein levels are lower, and even though C protein levels maintain stable, there is a resistance to the action of activated C protein. On the other hand, the placenta produces inhibitors of the plasminogen activator, which alters fibrinolysis³.

Venous stasis occurs as a result of the vascular compression exerted by the gravid uterus and the vascular dilation mediated by estrogens. A reduction in flow speed linked to an increase in diameter of the lower limbs' veins has been proven, which is more noticeable during the last trimester.

Finally, even though pregnancy does not cause endothelial damage itself, delivery does, more so if instrumentation or a C-section are performed. Said damage might be more intense if the pregnant patient previously smoked^{2,3}.

Diagnosis

DVT

Most of these DVT cases during pregnancy occur in the lower limbs, with a predisposition for the left lower limb (90%)^{1,10}.

The most common clinical data are acute onset of symptoms, erythema, pain, unilateral extremity heat and edema, lower abdominal pain, positive signs of hommas, and reflex arterial spasms, with cold and pale extremities, in addition to diminished pulses and difficulty with ambulation.

In the non-pregnant population, predictive clinical models such as the Wells score for DTV (Table 2) stratify patients to establish the possibility of having a thrombotic event, according to which they perform confirmatory imaging diagnosis. In the presence of a negative D-dimer (DD), the negative predictive value is 99.5%^{1,10}.

Additional studies include DD, which indicates a process of fibrinolysis subsequent to a thrombosis. Plasmatic levels are elevated in DVT and PTE, neoplasias, strokes, arterial thrombosis, disseminated intravascular coagulation, pneumonia, pregnancy, recent trauma, or hepatopathy. It increases during pregnancy, thus making it of little help, and its usefulness in pregnancy is still a topic of great debate⁹.

Imaging studies such as the Doppler ultrasonography are the standard method for the diagnosis of PVT. It is highly sensitive (92%) and specific (98%) for thrombosis¹¹. Contrast venography and impedance plethysmography have fallen into disuse and are not

Table 2. Wells score for deep venous thrombosis

Clinical characteristics	Score
Active cancer (treatment within 6 months or in palliative treatment)	+1
Paralysis, paresis, or lower extremity immobilization	+1
Bed rest for more than 3 days as a result of surgery (within 4 weeks)	+1
Localized sensitivity throughout the venous system distribution	+1
Edema in the entire leg	+1
Unilateral edema of the lower leg > 3 cm	+1
Orange-skin edema only in the symptomatic leg	+1
Non-varicose collateral superficial veins	+1
Alternative diagnosis at least as probable as DVT	-2
Total score	

Interpretation of risk score (probability of DVT), ≥ 3 points, high risk (75%), 1-2 points, moderate risk (17%), < 1 point, low risk (3%), DVT: Deep venous thrombosis.

always available for the detection of DVT¹². Magnetic resonance imaging (MRI) has a sensitivity between 94% and 96%, with a specificity of 90-92% for the detection of DVT; however, the use of intravenous gadolinium during pregnancy remains a topic of debate. It goes through the placenta and is classified as a category-C drug by the Food and Drug Administration of the United States and thus can only be used when the benefit is greater than the risk^{1,11}.

In summary, Doppler ultrasonography is recommended as an initial first-line test in pregnant women who are under clinical suspicion of DVT. If this study results positive, treatment ought to begin. In case of doubtful results, a venous MRI or venography with contrast should be performed as alternatives.

PTE

Early diagnosis of a pulmonary embolism during pregnancy is critical since there is a risk of a catastrophic maternal and fetal result if this is overlooked. If there is elevated clinical suspicion, empirical anticoagulation ought to be considered until the diagnostic process is complete. Similarly, a precise diagnosis is vital to avoid unnecessary treatment since this is linked to secondary effects in both the mother and the fetus.

Traditional clinical diagnostic keys of pulmonary embolism are dyspnea, tachycardia, tachypnea, pleuritic thoracic pain, and syncope. They are found in up to

Table 3. Wells score for PTE

Clinical characteristics	Score
Clinical symptoms of PTE	+3
Alternative diagnosis less probable than PTE	+3
Heart rate over 100 beats/min	+1.5
Immobilization or surgery within the past 4 weeks	+1.5
Previous PTE	+1.5
Hemoptysis	+1
Total score	

Interpretation of risk score (probability of PTE), > 6 points, high risk (78.4%), 2-6 points, moderate risk (27.8%), < 2 points, low risk (3.4%), PTE: Pulmonary thromboembolism.

90% of patients where a pulmonary embolus is shown. Nevertheless, these clinical signs and symptoms lack specificity and generate an ample differential diagnosis¹³. The most common clinical signs and symptoms are an acute onset of symptoms, dyspnea, tachypnea, pleuritic thoracic pain, hemoptysis, syncope, tachycardia, cyanosis, pleural rub, and a fixed S2.

In the non-pregnant population, predictive clinical models such as the Wells score for Pulmonary Thromboembolism (PTE) (Table 3) stratify patients to establish the probability of having thrombotic events, according to which, confirmatory imaging diagnostic tests are conducted. It has a sensitivity of 100% and specificity of 90 when the score is higher or equal to 6. However, it does not answer the questions among the pregnant population. Therefore, they ought to be taken to further studies¹⁴.

Additional studies include DD; however, just as in those patients suspected of DVT, it is sensitive but not specific regarding pulmonary embolism. With a negative predictive value of 95%, but only 25% specificity^{1,5}, the study of arterial gases can reveal hypoxemia, hypocapnia, and respiratory alkalosis¹.

Imaging studies such as Doppler ultrasonography show that approximately 70% of the patients with proven positron emission tomography (PET) have a proximal DVT^{1,5}. A chest film has little specificity and sensitivity for PET diagnosis. It can show unspecified alterations of the lung, parenchyma, atelectasis, pleural spilling, cardiomegaly, an elevated ipsilateral hemidiaphragm, pulmonary artery enlargement, and wedge-shaped perfusion defects^{1,14}. Pulmonary arteriography (PA) is considered the gold standard for PET diagnosis outside pregnancy, yet it is often used in high-risk cases which have negative compressive

ultrasounds. A negative PA excludes clinically relevant PET. Angiography through MRI, which utilizes an injection of gadolinium, has a global sensitivity of only 77% compared to pulmonary angiography (PA)¹⁵, and finally, helical computed tomographic (CT) PA is not sensitive for the diagnosis of subsegmental clots. Thus, CT-PA can fail to exclude smaller peripheral lesions¹.

An electrocardiogram can report a right bundle branch block, an axis displacement to the right, the presence of a Q wave in derivations II, III, and aVF, an S wave in derivations I and aVL >1.5 mm, inversion of the T waves in derivations III and aVF, or the presence of auricular fibrillation¹. The echocardiogram reports a hypokinetic and dilated right ventricle, tricuspid insufficiency, and dilation of the pulmonary artery, but it is useful only in 30-40% of the patients with PET when the transthoracic is performed and increases with the transesophageal echocardiogram, which has a sensitivity of 97% and a specificity between 88 and 100%¹.

DVT treatment in obstetrics

Treatment should begin as soon as the DVT or PET diagnoses are made and, in some cases, treatment ought to begin with the suspicion even before confirming the diagnosis⁵. The initial steps in the treatment of pulmonary embolism are oxygen therapy, stabilization of blood pressure, and evolution of the cardiovascular and respiratory states of the patient^{1,5,7}.

The main medical treatment is anticoagulation, and five different forms of treatment have been considered for the general population: Heparins, warfarin, surgery, vena cava filters, and thrombolytic therapy^{1,5,16}.

Heparins

These include unfractionated heparin (UFH), low molecular weight heparin (LMWH), and factor Xa synthetic inhibitors (fondaparinux). All forms of heparin are administered through an injectable route, either subcutaneously or intravenously^{1,5,6}.

Recommended schemes are as follows:

- Prophylactic UFH and subcutaneous (SC) UFH 5000 UI dose every 12 h.
- Adjusted-dose UFH, SC UFH every 12 h in adjusted doses until reaching an average interval in the partial time of thromboplastin within a therapeutic range (2-2.5 times the base value).
- Prophylactic LMWH, enoxaparin 40 mg SC every 24 h, bemiparin at a dose of 3500 UI SC every 24 h or dalteparin at a dose of 5000 UI SC every 24 h.

Dosage of two or three medications may vary in the extremes of the body mass index values.

- Therapeutic LMWH at a dose adjusted to body weight, enoxaparin 1 mg/kg every 12 h, dalteparin 200 U/kg every 12 h, both subcutaneously.

Warfarin

It is an anticoagulant indicated for long-term use outside pregnancy, which has been linked with fetal defects. Embryopathy caused by warfarin is linked to exposure at 6-12 weeks of gestation and increases the risk of loss of pregnancy, anomalies in the central nervous system, and risk of fetal and neonatal hemorrhage during delivery due to fetal anticoagulation. Therefore, for women receiving prolonged anticoagulation therapy who become pregnant, the use of UFH or LMWH in place of warfarin is recommended. However, warfarin is indicated in patients with mechanical heart valves, due to its high risk of thrombosis, and in the postpartum period if necessary, because there is no significant excretion in breast milk^{17,18}. When Vitamin K antagonists are used, an INR value of 2.0-3.0 should be achieved. At the beginning of the administration, it is administered simultaneously with heparin until they reach values in the INR ≥ 2.0 , and heparin is suspended.

Inferior vena cava filters

These are indicated when there are absolute contraindications for anticoagulant therapy (recent surgery, stroke, and active bleeding), adverse reactions or ineffectiveness of a previous anticoagulant (recurrent PET despite proper anticoagulation), or massive PET with significant compromise of the pulmonary vascular tree^{7,19}.

Surgery and thrombolytic therapy

Surgical embolectomy ought to be reserved for those situations which endanger life. Massive PET with hemodynamic instability constitutes the only indication for thrombolytic therapy during pregnancy, given the high risk of causing a placental abruption⁵.

General principles for VTE

- Therapeutic anticoagulation should last between 12 and 20 weeks.
- Prophylactic anticoagulation should begin after initial treatment, for 6-12 weeks and until the patient reaches 6 weeks after delivery.

- For complicated DVT, including those which affect iliofemoral vessels, prophylaxis for 4-6 weeks is recommended.
- Conversion to oral warfarin ought to be considered in the post-partum period, provided the patient accepts and complies with monitoring the level of medication.
- For patients with PET, prophylactic anticoagulation is recommended for 4-6 months.
- Maintain maternal partial pressure of oxygen above 70 mm Hg or oxygen saturation >94%.

Among pregnant patients who have had a previous VTE during pregnancy, a risk of recurrence of 2.4-10% has been reported.

When establishing if a pregnant woman requires the use of antithrombotic prophylaxis, in case they were not in treatment already, three main points must be taken into consideration^{20,21}.

- If the patient meets the criteria for prophylactic treatment, based on risk factors, concomitant pathologies, and pathological personal background.
- Risks and benefits of antithrombotic prophylaxis for the mother-fetus binomial.
- The mother's disposition toward the use of the indicated therapy.

Table 1 includes the criteria to establish which patients are at high risk of thromboembolic disease. If the patient meets at least one major criterion or two minor ones and requires an emergency C-section, they are considered a candidate for antithrombotic prophylaxis since the risk of Venous Thromboembolism (VTE) increases^{20,22-24}.

Unfractionated heparin and LMWH constitute the two options recommended for prophylactic therapy in pregnant women. Compared to UFH, LMWH requires a single application a day, it does not require strict monitoring with laboratory work, and secondary effects such as thrombocytopenia induced by heparin, osteoporosis, and allergic reactions are fewer^{20,21}.

Complementing the use of medications with anti-embolic averages or intermittent pneumatic compression is a recommended strategy for patients with a high risk of VTE who is in immediate surgical postpartum and in those patients where the risk factor for VTE persists during postpartum, maintaining anticoagulant up to 6 weeks after delivery²⁵.

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