








Deep Vein Thrombosis in Pregnancy: A Review Article

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Article Info	ABSTRACT
<p>Article type: Review article</p>	<p>Background and Aim: To date, numerous studies have evaluated the risk factors and treatment of venous thromboembolism (VTE) during pregnancy. The present study aimed to compile and present the latest guidelines related to the management and diagnosis of deep vein thrombosis (DVT) in pregnant women.</p> <p>Materials and Methods: In the present study, around 100 articles indexed from 2000 were retrieved from local and international databases using keywords, including "pregnancy", "DVT", "VTE", "anticoagulation", and "coagulopathy".</p> <p>Results: The current study examined the pathophysiology of DVT in pregnancy, risk factors, clinical signs, diagnosis, and treatment of DVT in pregnancy.</p> <p>Conclusion: Women during pregnancy and postpartum period represent one of the highest risk groups for DVT. The treatment and supportive measures are of paramount importance to reduce the risk and complications of this disease. Nonetheless, they are not devoid of serious challenges since the possible complications which can occur to the fetus and maternal health during pregnancy should be taken into account in treatment.</p>
<p>Article History: Received: 11 May 2020 Revised: 11 Aug 2020 Accepted: 16 Aug 2020</p>	
<p>Keywords: Deep Vein Thrombosis Pregnancy Upper Extremity Venous Thrombosis</p>	

➤ How to cite this paper

Tabaraii R, Farahmand H, Ahmadi Kohnali J, Rezvan S, Arjmandnia MH, Rezaei Naye M, Barati A, Yosefi M, Razavinia F. Deep Vein Thrombosis in Pregnancy: A Review Article. J Vessel Circ. Spring 2020; 1(2): 27-34. DOI: [10.21859/JVesselCirc.1.2.27](https://doi.org/10.21859/JVesselCirc.1.2.27)

Introduction

One of the challenges in the medical world today is venous thromboembolism (VTE) which is most commonly manifested as deep vein thrombosis (DVT) and pulmonary embolism (PE) (1). DVT refers to the formation of a blood clot in the deep veins of the lower and upper extremities (most frequently in the lower limbs), such as femoral and saphenous. These blood clots can travel to IVC, the right ventricle, and finally the bloodstream. They can block the veins and cause PE, if placed in the pulmonary artery. Therefore, DVT is recognized as one of the underlying causes of PE (2-5).

This issue assumes more importance in pregnant women, compared to non-pregnant ones. In this regard, according to published reports, pregnant women are more likely to develop DVT than PE (6). As evidenced by related studies, it inflicts 1 per 4 individuals (1), and the incidence of

DVT in pregnancy is 1 per 10,000 women (7). VTE is associated with various and serious complications unique to each form. For instance, PE is the leading cause of maternal death, while post-thrombotic syndrome (with symptoms of chronic leg pain, leg ulcers, edema) is more likely to develop in people who have DVT (6, 8-11).

Pregnancy alone can be considered a risk factor for VTE; moreover, some women run a higher risk of developing this disease. The most important risk factors for VTE during pregnancy include the previous history of VTE, acquired thrombophilia, previous history of VTE due to major surgery, medical problems (including cancer and heart disease), and high-risk hereditary thrombophilia. To date, numerous studies have been performed to evaluate the risk factors and treatment of VTE during pregnancy; nevertheless, it is not yet possible to

reduce the risk of DVT in pregnant women. Therefore, the current study aimed to compile and present the latest guidelines related to the management and diagnosis of DVT in pregnant women.

Materials and Methods

For the purpose of the study, the articles published within 2000-2019 were searched in the local and international databases, including PubMed, Science Direct, Scopes, and Google Scholar.

Search Strategy

The search was conducted in the title, abstract, and keywords of articles.

In the Advanced search section of the PubMed Database, 100 articles indexed from 2000 were retrieved using the keywords, including "Pregnancy", "DVT", "VTE", "Anticoagulopathy", "Coagulopathy" (google scholar=43, Pub med=27, Scopes=10, Science Direct=20), Persian and English full-text articles on the common topic of venous thrombosis and pregnancy. Important, new, and relevant articles were extracted and those which were not related to thromboembolism were removed. Finally, a total of 87 retrieved articles were used in the study.

Results

Deep vein thrombosis in pregnancy

One of the most common forms of VTE DVT which is 3 times more common than PE in pregnant women occurring in the third trimester of pregnancy and 6 months after delivery (12, 13). In general, the risk of VTE is 4 times higher in pregnant women than in non-pregnant women. In addition, the incidence of VTE increases in the first few months after childbirth in the case of vaginal delivery (1, 14).

Pathophysiology of deep vein thrombosis in pregnancy

Pregnancy is defined as a prothrombotic condition due to hormonal changes, and the risk of VTE increases 5-50 times due to specific risk factors during pregnancy, compared to non-pregnant women (17-15). An important theory about the pathogenesis of VTE, called Virchow's triad, proposes that VTE occurs as a result of three main causes: alterations in blood flow, vascular endothelial injury, and alterations in the hypercoagulable state)changes in hypercoagulation (18-20). The main risk factor for pregnancy-related VTE is hypercoagulopathy (1). Despite the marked decrease in fibrinolytic activity and the production of proteins C and S, fibrin production and levels of

coagulation factors II, V, VIII, and X increase during pregnancy. Following all the mentioned changes, it leads to a change in hemostatic state, which in turn, increases the D-dimer and F1+2 (8, 21, 22).

The anatomical condition of the lower extremities during pregnancy is responsible for 82% cases of thrombosis in the left lower extremity since the likelihood of DVT increases during pregnancy due to an increase in uterine size and external compression of the left common iliac vein by the right iliac artery (23, 24). During vaginal delivery, the risk of DVT increases by 6-11% following pelvic vein endothelial damage due to Valsalva maneuver or venous hypertension (23, 25). Extensive studies conducted on the status of thromboembolism in pregnant women revealed that 50% of the reported cases are related to the gestational age of 25 to 29 weeks and 6 weeks after normal delivery (24).

Deep vein thrombosis risk factors in pregnancy

In general, VTE risk factors fell into three categories: acquired, genetic, and mixed. Acquired factors can be assigned to medical, pharmacological, and behavioral categories for more detailed investigation. More details are presented in Table 1. The risk factors for VTE during pregnancy can be classified as definite and probable. For instance, the main risk factors for DVT in pregnancy include a history of unexplained thrombosis, the use of estrogen (such as oral contraceptives) before pregnancy, as well as some diseases, such as lupus, antiphospholipid syndrome, and heart disease (1, 9, 10, 20, 23, 26-31).

Clinical symptoms of Deep vein thrombosis in pregnancy

The main clinical symptoms of DVT in pregnant

Table 1. Risk factors for venous thromboembolism

Previous venous thromboembolism
✓ History of taking oral contraceptives
✓ Premature birth
✓ Smoking
✓ Preeclampsia
Varicosities
✓ Cesarean section (especially in an emergency)
✓ Vomiting during pregnancy
Infection or bleeding after childbirth
✓ Severe thrombophilia
✓ Blood transfusion
Assisted reproductive technology
✓ Immobility
✓ BMI more than 30 kg per square meter
✓ Systemic lupus erythematosus
✓ Antiphospholipid syndrome
✓ Cardiovascular diseases

women include discomfort (with a prevalence of 79% and 95% during pregnancy and postpartum, respectively), edema in the lower extremities (with a prevalence of 88% and 79% during pregnancy and postpartum, respectively) (8, 23, 32, 33). Other symptoms of DVT entail abdominal pain, pain in the back, and swelling of the whole leg (8, 23) which is more common in isolated iliac DVTs, compared to other veins (24, 34). It should be noted that in most cases, these symptoms are not examined due to overlap with discomfort and swelling in the leg; therefore, they do not give rise to the suspicion of isolated iliac DVT.

Sometimes the symptoms are so mild that they are not treated on time, rather they attract the attention of physicians with pain and edema all over the leg due to the spread of thrombosis in distal veins, such as the femoral vein (24). Therefore, DVT should be taken into account when dealing with pregnant women who suffer from such symptoms as edema and pain. Moreover, necessary diagnostic tests are needed to minimize the risk of embolic complications and post-thrombotic syndrome by timely identification and treatment.

PE occurs when a blood clot that develops in a blood vessel in the body break loose, travel through the bloodstream, and block an artery in the lungs (2, 4). About 40-50% of PE episodes are asymptomatic without any symptoms during pregnancy (8). Nonetheless, due to the serious complications of PE, such as hemorrhage, renal failure, and maternal death, early diagnosis and treatment of PE is of utmost importance (1). Post-thrombotic syndrome refers to a set of symptoms, such as chronic leg pain, edema, and leg ulcers, which occur after thrombosis. According to a case report, the prevalence of the post-thrombotic syndrome is 42% in pregnant women with a history of DVT (26, 35).

Increased thigh circumference is one of the most commonly used diagnostic tests and reliable symptoms to confirm DVT. The results of a meta-analysis showed that patients with a difference in thigh circumference leg diameters were twice as likely to develop DVT. Homan's sign (discomfort behind the knee upon forced dorsiflexion of the foot) is not reliable for the diagnosis of DVT (7).

Diagnosis of deep vein thrombosis in pregnancy

It is noteworthy that routine laboratory tests, such as complete blood count (CBC), blood chemistry tests, kidney function tests, and coagulation profile, are not practical factors for the diagnosis of DVT. They can merely be regarded as effective clues to identify the underlying cause and treat DVT after definitive diagnosis. Therefore, at

the suspicion of DVT, the following methods can be used and diagnostic procedures can be performed according to the protocol.

Compression ultrasonography

Compression ultrasound is one of the most valuable diagnostic tests for DVT in the general population (both pregnant and non-pregnant). It has a sensitivity and specificity of 97% and 94%, respectively. Advantages and disadvantages of compression ultrasonography include cost-effectiveness, safety, and non-diagnosis of pelvic vein thrombosis (24). Compression ultrasound is also one of the practical methods for the diagnosis of DVT in pregnancy, which can detect this disease by preparing a graph of compressible and non-compressible veins (due to thrombosis) (26). A timely compression ultrasound examination is considered a key point in minimizing the risk of PE. Although compression ultrasonography is a very practical method, it is recommended that the iliofemoral vein be separately examined by D-dimer (6, 26).

Compression ultrasonography yields two general results 1) a positive result: a definitive diagnosis of DVT is made and then treatment can be started. A negative result: a) in case of high clinical suspicion of DVT or thrombosis in a limited area, compression ultrasound can be performed serially on the third and seventh days. In this regard, the iliofemoral vein should be examined to make a definite diagnosis of DVT. b) limited examination, c) clinical signs of low back and hip pain, and clinical suspicion of DVT in the iliac vein. In these cases, the possibility of DVT can be assessed using venous magnetic resonance imaging (MRV) or venography (1). In general, single or serial compression ultrasonography is one of the most repeatedly used diagnostic methods in hospitals (6).

Magnetic resonance or contrast venography

Magnetic resonance or contrast venography is one of the practical tests for the diagnosis of DVT in pregnant women. It is used at the event of a negative compression ultrasound test (both single and serial) and such clinical symptoms as back and hip pain that lead to increased clinical suspicion of DVT (1).

D-dimer

D-dimer is a fibrin degradation product that is elevated (highly sensitive) in almost all patients with acute DVT (2). However, it is worth noting that this increase is not inclusive to DVT, rather the D-dimer levels are raised in other conditions, such as malignancy, sepsis, recent surgery or trauma, and

renal failure (36-39). Nevertheless, studies have always demonstrated high sensitivity and low specificity of D-dimer in patients with acute DVT. However, threshold levels and D-dimer evaluation methods vary in different laboratories (40-42).

It is especially important that the D-dimer test should not be performed as the sole basis for diagnosis in patients with suspected DVT, rather it but should be used in combination with clinical pretest probability (PTP) and/or ultrasound (43-45).

As a matter of principle, the tests that are highly sensitive to diagnose DVT are likely to yield more accurate results in patients with low to moderate clinical suspicion. They are useful in case of yielding negative result for DVT (46) and has very limited efficacy in patients with high clinical suspicion due to diagnostic value (47).

The measurement of D-dimer levels in the blood is one of the tests most frequently used to diagnose DVT in pregnant women (26). It should be noted that due to physiological conditions during pregnancy, the D-dimer level in the peripheral blood increases, which is considered a false positive (47). However, in conditions, such as early pregnancy, when the physiological conditions are more similar to the time before pregnancy and have not undergone considerable change, the D-dimer test is a useful and practical method for the diagnosis of DVT in pregnancy (46).

Wells scoring system

The most practical clinical method used to determine the likelihood of DVT is the Wells scoring system (1, 48-52). The details of this system are presented in Table 2. However, the guidelines and reports in the present articles do not consider the Wells scoring system to be a reliable test for pregnant women. It is considered neither a risk factor for DVT nor an appropriate and practical test to assess the likelihood of pregnancy-related DVT (6).

Treatment of deep vein thrombosis in pregnancy

The management and treatment of DVT during

pregnancy is one of the most important and challenging issues in healthcare. Patient management decision-making also poses daunting challenges due to possible complications which threaten both mother and fetus. Inappropriate medication use is associated with very important side effects, such as bleeding during vaginal birth, embryopathy, or fetal hemorrhage. Therefore, several basic principles should be taken into account when using treatment regimens for pregnancy-related VTE. These principals include: 1) the proper efficacy of medication regimen, 2) safety of the regimen for mother and fetus, 3) ability to use medication regimen for primary and secondary treatment of thrombosis during pregnancy and postpartum (30). The following section presents a brief explanation of the treatment methods used during pregnancy.

Anticoagulants

Anticoagulants are first-line medications used in VTE in all patients except high-risk patients, such as patients with a history of recent major surgery (26). In general, anticoagulants used in the prevention and treatment of VTE (in all patients) include heparin and heparin-like drugs (such as unfractionated heparin (UFH), low molecular weight heparins (LMWH), danaparoid sodium, and pentasaccharide (30). Anticoagulants are one of the most effective medications used in DVT diagnosed in pregnant women to prevent the resultant effects. Nevertheless, each medication has its unique advantages and disadvantages during pregnancy which must be taken into account when choosing a drug.

Low molecular weight heparin

One of the effective and widely used medications in pregnant women is low molecular weight heparin (LMWH) which has no significant side effects since it does not cross the placenta which is the portal for entry of drugs into the mammary ducts (53). According to international guidelines, the minimum duration necessary for treatment with LMWH is 3 months. However, for DVT during pregnancy, it is recommended that treatment continues until the end of pregnancy and also 6 weeks after delivery (1). According to the DVT Management Guidelines, LMWH does not require anti-Xa monitoring in all pregnant women, and the only group who need anti-Xa monitoring are those who weigh less than 50 kg or more than 90 kg (6).

As illustrated by conducted studies, in special circumstances when the use of LMWH is not allowed and it is associated with side effects, you can use an alternative medicine called

Table 2. Wells scoring system

Variable	Score
Previous PE or DVT history	+1.5
Heart rate > 100 beats per minute	+1.5
Recent surgery or prolonged immobility	+1.5
Clinical signs of DVT	+3
Hemoptysis	+1
Cancer	+1
Detection of alternatives less similar to PE	+3
Probability of PE	Score
High	4≤
Low	6>
	Prevalence of PE
	7.8%
	61%

DVT: Deep vein thrombosis, PE: Pulmonary embolism

fondaparinux, which is a direct inhibitor of factor Xa and cannot cross the placenta (6, 54, 55). Unlike LMWH, Warfarin is one of the well-known vitamin K antagonists which can cross the placenta and cause very serious complications, such as fetal death, fetal hemorrhage, and teratogenicity. It is noteworthy that the use of vitamin K antagonists (heparin and warfarin) is contraindicated during pregnancy, and the use of vitamin K antagonists is unrestricted after childbirth (even during breastfeeding) (6).

Other medications

To date, no guidelines have been suggested for the use of anticoagulants, except for vitamin K and LMWH antagonists, such as factor Xa inhibitors (rivaroxaban), during pregnancy and even lactation (1).

Compression stockings

Compression stockings are one of the best treatments to reduce pain and edema caused by DVT. Studies have shown that periodical compression (caused by body weight) on the plantar venous networks results in normal movement and increased venous blood flow in the leg and sole (65). The mechanical venous pump in the foot can establish periodic venous pressure as a physiological mechanism in hospitalized patients (55).

According to previous studies, this method of thromboprophylaxis has been effective in patients with acute fractures, joint arthroplasty, or knee arthroplasty (56, 57). However, in a meta-analysis study conducted by Subbiah R et al. (2016), no significant relationship was observed between the use of compression stockings and reduction of post-thrombosis syndrome, compared to the control group at the confidence level of 0.27 to 1.16 ($P = 0.12$) (58).

Inferior Vena Cava filters

Inferior Vena Cava Filters (IVC) filters are placed via the contralateral femoral vein and enter the Vena Cava. This device can catch blood clots from the legs before they reach the lungs and effectively prevent pulmonary embolization. This method is the definitive choice for patients with risk factors for DVT, such as stroke, recent hemorrhage history, or active hemorrhage, who are under anticoagulant therapy. In addition to the abovementioned advantages, this method is associated with potential complications, such as death due to proximal coagulation, which makes decision-making difficult in this regard (59, 60).

Although no guideline exists to confirm the use of IVC filters, one of the benefits of IVC filters is the prevention of PE (24). Regarding the indications for the use of IVC filters during

pregnancy, it can be related to certain conditions, such as contraindications to anticoagulants, increasing growth of thrombosis in the near-term period of delivery, and recurrent venous thromboembolism, which should also be temporarily implanted (61, 62).

Discussion

Assiduous attention to gestational age is one of the basic principles of DVT management (1). Initially, the patient should be provided with the necessary instructions for the treatment process. For instance, before the commencement of any medication regimen, the patients should be instructed to use the medication regimen. Be sure to discontinue LMWH at least 24 h before anesthetics injection for cesarean section. If you notice any signs of normal labor, stop the heparin injection, and never remove the catheter earlier than 12 h after LMWH injection.

Note that the choice of the treatment regimen is based on the patient's condition, and it is necessary to start the LMWH regimen 2-4 weeks before delivery and replace it with intravenous heparin at 38 weeks of gestation. Moreover, intravenous heparin injection should be stopped 6 h before delivery. At the event of venous thrombosis in late pregnancy (more than 38 weeks of gestation), the best treatment is intravenous heparin or IVC filters.

One of the preferred postpartum treatments is the replacement of LMWH, or unsaturated heparin (UFH) with IVC filters. In general, each of the abovementioned methods should be selected based on gestational age since it contributes greatly to the success of treatment (63). The placement of IVC filters requires radiation which gives serious cause for concern due to radiation-related side effects. As indicated by the Radiology Advisory Committee, radiation less than 100 mGy is not associated with any significant side effects. According to a retrospective study that examined the doses used to place IVC filters, the average dose used was reported to be less than 100 (67.55 mGy). Consequently, the dose used for the placement of IVC filters is not accompanied by any serious adverse effects (64).

Conclusion

Women during pregnancy postpartum are one of the high-risk groups for the development of VTE. Although the treatment and supportive measures needed to reduce the risk and complications of this disease are very valuable, they are not devoid of serious challenges since considering the possible complications to the fetus and maintaining the general well-being of the mother during pregnancy are the main principles of decision making to treat

patients. Despite the advancement of medical science and the introduction of numerous safe and applicable methods, such as IVC filters and catheters, there carry their own problems and complications.

Further studies and investigations, as well as information provision and awareness-raising among pregnant women, are the keys to the success of therapeutic and supportive measures with minimum adverse effects. It is due to the fact that timely referrals and more appropriate decisions lead to the reduction of fetal and maternal complications during pregnancy and postpartum.

Acknowledgments

We thank Ms Mojdeh Vaezzadeh for her cooperation in the following project.

Conflicts of interest

None.

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