

VENOUS THROMBO-EMBOLISM DURING PREGNANCY AND POSTPARTUM PERIOD

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Abbreviation

Venous thromboembolism (VTE), deep venous thrombosis (DVT), pulmonary embolism (PE), unfractionated heparin (UFH), low molecular weight heparin (LMWH)

INTRODUCTION

Deep vein thrombosis (DVT) & pulmonary embolism (PE) are different aspects of same pathologic process which is coined venous thromboembolism (VTE). VTE is a leading cause of morbidity and mortality during pregnancy. It has been reported to complicate 1 in 1000 to 2000 pregnancies. The risk is present during pregnancy and over post partum period in 0.5 to 3% of pregnancies¹. Deep venous thrombosis is the most common type of VTE out of which 70-90% occurs in ileo-femoral vein in left leg². If venous thrombosis

remains untreated, 15-24% of these patients will develop pulmonary embolism (PE). PE during pregnancy may be fatal in almost 15% of patients and in 66% of these, death will occur within 30 minutes of embolic event³. In Indian settings DVT is often unnoticed in pregnancy and postpartum period. Thus it usually presents with dreaded complication i.e. pulmonary embolism. Awareness of this disease in our day to day clinical practice will help in preventing VTE in at risk patients.

PATHOPHYSIOLOGY

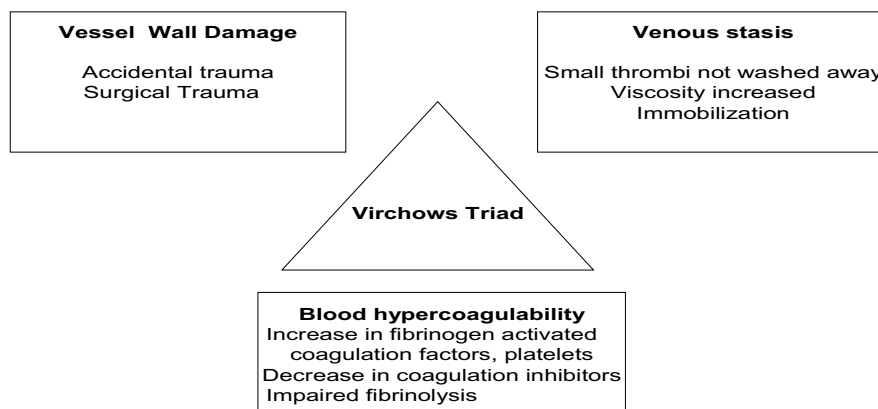


Figure 1: Classic Virchows triad for factors predisposing for VTE

A normal pregnancy induces a hyper-coagulable state. The hematologic changes in pregnancy include increased circulating levels of clotting factors as well as changes in fibrin generation and fibrinolysis. Circulating levels of multiple clotting factors including factors I, II, VII, VIII, IX and X have been shown to be elevated in pregnancy and the puerperium. The

generation of fibrin is also increased and fibrinolytic activity is decreased.

Progesterone mediated increases in venous distensibility and capacity is apparent in first trimester and result in increased venous stasis. Pregnancy related deep venous thrombosis have remarkable left side predominance and although the exact mechanism is

not known, it is likely due to more significant stasis in the left sided venous system. During pregnancy, the right iliac artery has a compressive effect of the left common iliac vein.

Late third trimester and immediate post partum are the highest risk factor for VTE; but with changing

obstetrics practice like early ambulation after delivery, there is a decrease in VTE in this period. However due to subtle clinical presentation, risk of undetected VTE in early and mid trimester pregnancy has increased^{3,4}.

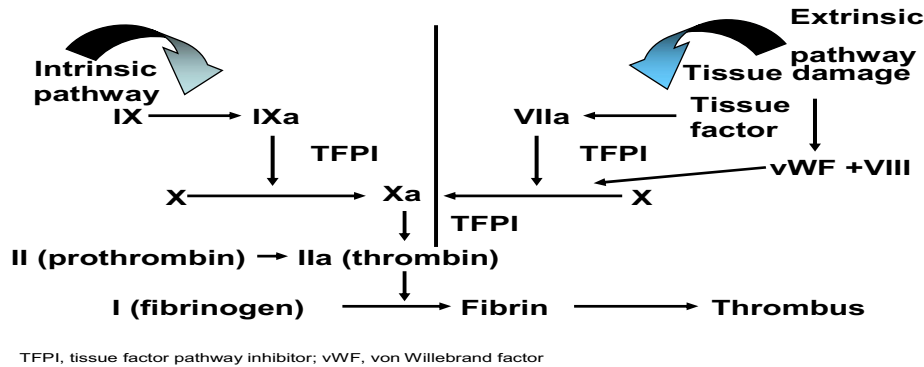


Figure 2: Normal Coagulation Cascade

RISK FACTORS

The factors which increase the risk of venous thromboembolism in pregnant patients are age more than 35, multiple gestation, parity>4, pre-eclampsia, varicose veins, obesity, cesarean section, previous VTE, spinal cord injury with paraplegia, major abdominal surgery, family history of VTE and patients with inherited thrombophilias (like antithrombin deficiency, factor V deficiency, Protein C and S deficiency, myeloproliferative disorders).

New onset or transient risk factors may be added during pregnancy and post partum like surgical procedure in pregnancy or puerperium, hyperemesis, dehydration, ovarian hyperstimulation syndrome,

severe infections (pyelonephritis), immobility (> 4 days of bed rest), pre-eclampsia, excessive blood loss, long haul travel, prolonged labour, instrumental delivery and immobility after delivery⁵.

Screening for such inherited thrombophilias should be done in patients with a history of thrombosis, unexplained fetal loss at 20 weeks of gestation or longer, severe preeclampsia/ HELLP at less than 34 weeks gestation, severe IUGR or a positive family history. The tests include factor V leiden mutation, prothrombin G20210A mutation, functional protein C and S deficiencies, AT III deficiency, lupus anticoagulant, homocysteine level and anticardiolipin antibodies⁵.

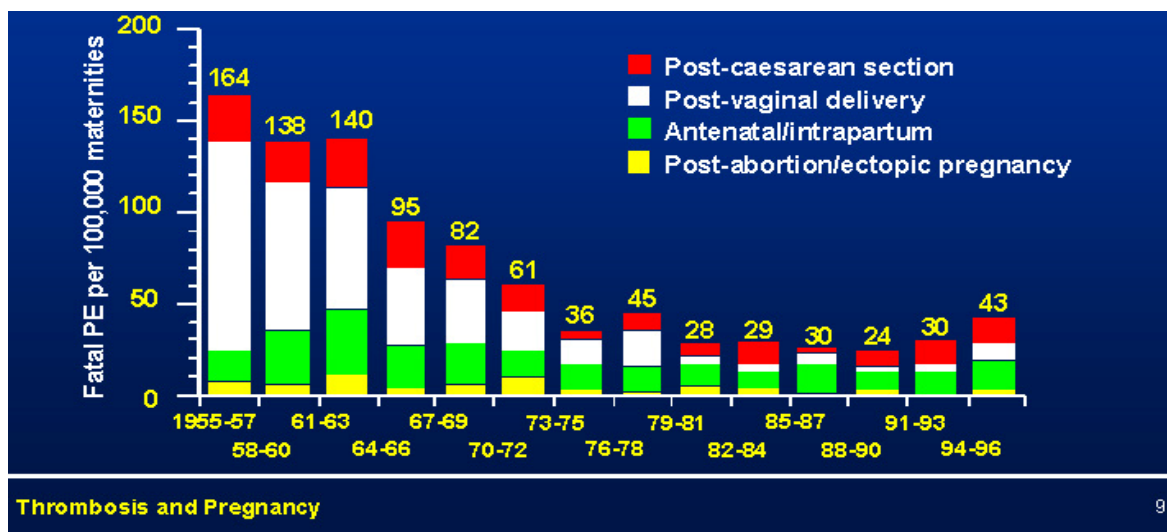


Figure 3: Incidence of Fatal PE in UK

DIAGNOSIS

Timely diagnosis of deep venous thrombosis is crucial because up to 24% of patients with untreated DVT will develop pulmonary embolism. High index of suspicion is important to differentiate clinically as many of the clinical features of thromboembolism including tachycardia, dyspnea leg pain and swelling may also be associated with normal pregnancy. Diagnosis can be confirmed with objective testing.

Common clinical features of DVT include lower extremity edema, pain, and difficulty with ambulation, warmth and erythema. Diagnostic tests for evaluation of suspected DVT include D dimer assays, venous colour doppler ultrasound, magnetic resonance venography, CT and contrast venography.

D dimer is a product of degradation of fibrin by plasmin. It has low specificity for pulmonary embolism as it is elevated in pregnancy and even in post partum period. D dimer has a higher negative predictive value; i.e. a negative test along with low clinical probability virtually rules out DVT or pulmonary embolism. Compression venous ultrasound with color Doppler is very sensitive and specific to detect proximal DVT (common femoral, superficial femoral, greater saphenous and popliteal veins). It is cost effective non invasive means of diagnosis. It is less sensitive and specific for distal thrombosis. Although MR venography is more superior in diagnosing DVT, experience in pregnancy is limited. Contrast venography is seldom used nowadays because of invasive nature and availability of superior non-invasive tests^{6,7}.

Clinical features of pulmonary embolism include breathlessness, dry cough, chest discomfort, perspiration, cyanosis and signs of shock if embolism is massive. CT pulmonary angiography is the gold standard to diagnose pulmonary embolism. 2 D Echo detects right ventricular dysfunction secondary to sub-massive or massive PE. X ray chest and ECG are non specific modalities; sinus tachycardia being the most common ECG pattern seen^{8,9}. In pregnant patient with high likelihood of pulmonary embolism the benefits of diagnosing this fatal and easily treatable disease outweighs the risk of radiation to fetus.

TREATMENT

Acute thromboembolism in pregnancy requires immediate medical management¹¹. The mainstay of management is optimum anticoagulation. The agents used are either low molecular weight heparin (LMWH) or unfractionated heparin (UFH) as they do not cross the placental barrier. Due to risk of teratogenicity, warfarin is contraindicated in pregnancy.

Agents used

UFH dose is adjusted by monitoring aPTT and is kept around 1.5 to 2 times the normal¹². The dose in pregnant patient tend to be higher because of increased circulating levels of heparin binding proteins, increased plasma volume, increased renal clearance due to

increased glomerular filtration and increased heparin degradation by the placenta. The complications of heparin therapy include maternal hemorrhage, heparin induced thrombocytopenia and heparin induced osteopenia. Bleeding risk is not increased as compared to non-pregnant patients. In certain rare circumstances like patients who are hemodynamically unstable due to massive PE, patients at risk of bleeding (immediate post operative patients) and patients with antepartum placental abnormalities, UFH is preferred due to shorter half life and ease of reverting the action with protamine sulphate⁹.

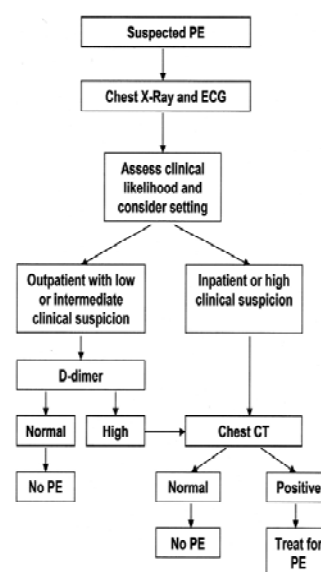


Figure 4: Diagnostic approach for Pulmonary Embolism (PE)¹⁰

Intravenous heparin is used initially in the management of VTE with a loading dose of 80U/Kg followed by continuous infusion of heparin adjusted to aPTT monitoring every 4-6 hourly. Once a steady state is achieved, then aPTT is monitored once daily. DVT can also be treated with subcutaneous dose heparin to maintain aPTT at 1.5 times the control value. Ideal duration of anticoagulation therapy in pregnant patient is uncertain but American college of obstetrics and gynecology recommends therapeutic subcutaneous heparinization for 3-4 months followed by prophylactic or mini-dose heparin throughout pregnancy and for 6-12 weeks postpartum^{13,14}.

Low molecular weight heparins (LMWH) are better as compared to UFH in terms of lower incidence of HIT, more predictable dose response, they do not cross the placental barrier, less incidence of hematoma at injection site and lower incidence of osteopenia. When LMWH is given on a weight adjusted basis, dose response is predictable and reproducible^{15,16}. Routine laboratory monitoring of dose of LMWH is not warranted. Although in special cases dose should be titrated with anti-Xa levels in very high risk cases. This is difficult in Indian setting as this is not routinely

available. The agents used in pregnancy are enoxaparin and dalteparin.

Coumarin derivatives are contraindicated in pregnancy due to risk of embryopathy, anticoagulant effect on fetus and subsequent fetal hemorrhage¹⁷. Warfarin has to be titrated with INR (international normalized ratio). If warfarin is used during pregnancy, pregnant women should be counseled about the risk. Heparin should be substituted for the last 2-4 weeks of pregnancy. In post partum period, warfarin can be given with initial overlap with heparins till INR is between 2.0 - 3.0¹⁶.

The use of **low-dose aspirin** (75 mg daily) may be appropriate in situations where the risk of VTE is increased but is not deemed high enough to warrant the use of antenatal LMWH; for example, in women with previous provoked VTE without thrombophilia. Women should be advised of the lack of evidence for benefit of aspirin use for thromboprophylaxis in pregnancy⁵.

Graduated elastic compression stockings may be used antenatally. Thromboelastic stockings are appropriate for hospital inpatients at increased risk of VTE and may be combined with LMWH. Their use is also recommended for pregnant women traveling by air.

Treatment protocol⁵

Intensity and length of VTE prophylaxis in pregnancy depends on the patients' history of VTE. It is recommended that pregnant women with a **single previous VTE event secondary to a transient risk factor** have clinical surveillance for signs and symptoms of VTE and receive 4 to 6 weeks of postpartum prophylaxis with LMWH (enoxaparin 40 mg or dalteparin 5000 IU daily) as a single agent therapy or cross over to warfarin (dose to achieve an international normalized ratio (INR) of 2-3). When the initial VTE event was **secondary to prior pregnancy, estrogens, or additional risk factors (obesity) or was a single idiopathic VTE event** (and patient is no longer on long term anticoagulation), then antepartum prophylaxis is recommended with LMWH (enoxaparin 40 mg or dalteparin 5,000U daily) followed by post partum prophylaxis as noted above. If the VTE event was **secondary to thrombophilia or there is a strong family history of thrombotic events and a personal history of VTE**, we recommend unfractionated heparin in mini (5000U S/C BD) or moderate dose (5000U S/C TDS), intermediate dose or LMWH (Dalteparin 5000U or enoxaparin 40mg twice daily) plus post partum prophylaxis. Similarly women with **antithrombin deficiency, prothrombin gene mutation or factor V leiden mutation with a history of VTE** should receive intermediate dose LMWH with postpartum prophylaxis for 4 to 6 weeks. For patients with **multiple episodes of VTE** receiving long term anticoagulation with warfarin, the warfarin should be discontinued and full weight adjusted LMWH started. In the postpartum period, cross over

to warfarin is recommended until an INR of 2.0 to 3.0 is achieved.

Care during labour and delivery during anticoagulation⁵

The pregnancy associated prothrombotic changes in coagulation system are maximal immediately following delivery. Therefore, it is desirable to continue LMWH during labour or delivery in women receiving antenatal thromboprophylaxis with LMWH. For woman receiving high prophylactic or therapeutic doses of LMWH, the dose of heparin should be withheld if the woman goes into labour or reduced to its thromboprophylactic dose on the day before induction of labour or elective caesarean section and continued in this dose during labour. If woman is of normal weight, the dose for unfractionated heparin should be 5000 U 12 hourly. For LMWH preparations, a once a daily regimen should be adopted using the following doses: enoxaparin 40mg or dalteparin 5000IU.

Epidural anaesthesia can be sited only after discussion with the anesthetist. It is important to discuss the implication of treatment with heparin or LMWH for epidural or spinal anaesthesia with woman before labour or caesarean section. To minimize the risk of epidural haematoma, regional techniques should not be used until at least 12 hours after the previous prophylactic dose of LMWH. When a woman presents while on a therapeutic regimen of LMWH, regional techniques should not be employed for at least 24 hours after the last dose of LMWH. LMWH should not be given for at least four hours after the epidural catheter has been inserted or removed and the cannula should not be removed within 10-12 hours of most recent injection.

For delivery by elective caesarean section, the woman should receive a thromboprophylactic dose of LMWH on the day before delivery. On the day of delivery, the morning dose should be omitted and the operation performed that morning. The thromboprophylactic dose of LMWH should be given by three hours postoperatively (or four hours after insertion or removal of the epidural catheter, if appropriate). There is an increased risk of around 2% of wound hematoma following caesarean section with both unfractionated heparin and LMWH.

Woman at high risk of hemorrhage with risk factors including major antepartum hemorrhage, coagulopathy, progressive wound Hematoma, suspected intraabdominal bleeding and postpartum hemorrhage may be more conveniently managed with unfractionated heparin. Unfractionated heparin has a shorter half life than LMWH and there is more experience in the use of protamine sulfate to reverse its activity. If a woman develops a hemorrhage condition while taking LMWH, the treatment should be stopped and expert haematological advice sought. It should be remembered that excess blood loss and blood transfusion are risk factors for VTE, so thromboprophylaxis should be commenced or reinstated as soon as immediate risk of hemorrhage is reduced.

Thrombolysis in Pulmonary Embolism¹⁸

Thrombolytic therapy should be considered in pregnant patients only in cases of massive pulmonary embolism with hemodynamic instability or patients with massive embolism on CT scan and signs of right ventricular dysfunction. The agent of choice is either streptokinase or recombinant tissue plasminogen activator as they do not cross the placental barrier. There are very few case studies till date for the safety of thrombolytics in pregnancy; but given the risk of maternal death, use of thrombolytics is justified. The bleeding risks are found to be comparable to non-pregnant levels¹⁹.

Prevention

Patients who have risk factors for VTE should be counseled during pregnancy about possible symptoms and they should be initiated on preventive modalities. Those with low risk factors like family history, severe preeclampsia, IUGR, fetal loss at ≥ 20 weeks, obesity should be given anti-thrombotic compression devices. Those with highest risk like previous VTE, anti-phospholipid antibody syndrome, inherited thrombophilias, prolonged immobilization should be started on pharmacological support. Enoxaparin (40 mg S/C OD) or Dalteparin (2500U S/C OD) should be started in antepartum period and they should be switched over to coumarins in the post partum period^{12,20}.

SUMMARY

Venous thromboembolism during pregnancy is one of the dreaded emergencies. Early diagnosis and prompt treatment is the key to prevent maternal morbidity and mortality. Heparins are the mainstay of treatment. All pregnant women with risk factors should be counseled for sign and symptoms of VTE. Low threshold for initiating treatment should be practiced in such cases. Studies are needed from Indian settings to understand the true incidence, natural course and treatment response of VTE in pregnancy.

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