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# VENOUS THROMBOEMBOLISM IN PREGNANCY; CURRENT UPDATE

Gynaecology

**Dr Roshini Ambat*** MD DGO Senior Consultant Obstetrics and Gynaecology, KIMS Trivandrum *Corresponding Author

**M/s Gayathri Ananyajyothi Ambat** MBBS Student GIMSR, GITAM.

**Prof Dr Radhakrishnan Pradeep Kumar** Mch CTVS AIIMS, Postdoctoral Fellow, Chief Division of Cardiothoracic Surgery, GIMSR, Gitam University,

**Dr Nihaz Nazer** Junior Resident CTVS, Travancore Medical College Hospital

**Prof Dr Nazer** Prof Chief Division of Cardiothoracic Surgery, Travancore Medical College Hospital, Kerala.

## ABSTRACT

Two decades have witnessed paradigm shift in the management of venous thromboembolism in pregnancy. Traditional conservative treatment has paved way for more aggressive and minimally invasive treatment protocols. This article takes a fresh look at current management strategies.

## KEYWORDS

VTE, DVT, PE, CUS, MRI, LMWH, UFH, PERT

## INTRODUCTION

Prevalence of venous thromboembolism is 1/600 (1-4).It is important to consider the condition for proper diagnosis and treatment. Local or embolic features like pulmonary embolism may be the presenting features. Pulmonary embolism is the 7th leading cause of maternal mortality causing 9%of maternal deaths (5, 6).Epidemiology pathogenesis diagnosis prevention and treatment will be discussed in this article.

### Epidemiology

Incidence of venous thromboembolism is around 1 in 500-2000 pregnancies(7).DVT is three times more common than pulmonary embolism (8).Incidence of pulmonary embolism is 0.15 per 1000 deliveries with 0.07 being antenatal and 0.08 being postnatal (9).Black women have a 3-4 times higher mortality compared with white women and a higher incidence is noted in Asian women also with an odds ratio of 1.5 (10).Increased recognition of this condition with appropriate use of Thromboprophylaxis in postpartum period had decreased the incidence but increase in co morbidity in the general population like obesity and hypertension causes a reversal of this trend (11)

### Risk Factors

These are summarised in Table 1.Pregnancy increases the DVT risk up to 50 times compared with non pregnancy women (12).Greater prevalence is noted in the left side compared with right. European studies point to emergency caesarean section, stillbirth, varicose veins, pre-eclampsia/eclampsia, postpartum infection, and co morbidities being associated with increased risk though further validation is needed in this respect(7). First and third trimester shows increased risk of VTE (13).Well recognised antepartum risk factors includes multiple births, varicose veins, inflammatory bowel disease, maternal age more than 35 years, BMI of more than 30kg/m2,more than 3 days hospitalisation for non delivery reasons, diabetes and urinary tract infection. Post partum risk factors – with highest incidence in the first 6 weeks -recognised includes post partum infections, smoking, increased maternal age ( above 35 years),obstetric haemorrhage, BMI more than 25kg/m2, medical co morbidities( like varicose veins, cardiac disease, inflammatory bowel disease),caesarean section ( emergency),young gestational age (less than 36 weeks),still births, hypertension, smoking, eclampsia or preeclampsia ( 14,15,16).Risk is augmented in those with inherited thrombophilias (17,18).See Table 2.Factor V Leiden deficiency increases the risk three times that is augmented by G20210A prothrombin gene mutation up to 50 fold (18).
Pathogenesis

Stasis is due to compression of large veins by gravid uterus and the linear flow velocity in the lower extremity veins being decreased because of hormonally induced dilation of capacitance veins, leading to venous pooling and valvular incompetence (19). Reduced flow velocity in the left common femoral vein and inferior vena cava that was most evident in the supine position. Compression of the left iliac vein by the right iliac artery contributes to DVT during pregnancy. Reasons for endothelial damage includes injury and changes at the utero placental surface. Forceps, vacuum extraction, or surgical delivery exaggerates intimal injury (20).Elevation of coagulation factors I, II, VII, VIII, IX, X, along with a decrease in protein S induces a hypercoagulable state. Protein C elevation is noted in second and third trimesters. A high resistance to activated protein C is also noted. Fibrinolytic inhibitors PAI-1 and PAI-2 is increased during pregnancy (21).

Clinical Features
Signs and symptoms are listed in Table 3.
Pain
Swelling
Erythema
Warmth
Tenderness
Swelling of entire leg with iliac thrombosis
Back pain
Left sided (70-90%) and femoral vein involvement more common
Hofman's sign
May Thurner syndrome
Pelvic vein also involved
Breathlessness, circulatory collapse

Predictive scoring systems like Wells score, LEFt clinical prediction rule and D Dimer levels all need further validation in use in pregnant population.

Lab Tests
Negative D Dimer is useful test especially when combined with negative ultrasound. As D Dimer levels increases in pregnancy validation by more prospective studies is needed to accept higher cut off values( > 500ng/ml by ELISA) being used as positive diagnostic tool (22).

Compressive Ultrasound Scans: Poor Compressibility.
MRI Venography – negative filling defects.
Doppler evaluation- poor flow in iliac veins
Serial CUS for progression mapping

Ascending Contrast Venography with concerns about foetal exposure to ionizing radiation, technical difficulties of femoral vein cannulation, and decreased sensitivity for isolated iliofemoral thrombosis due to abdominal-pelvic shielding makes CUS a more preferred investigative modality.

Inherited or acquired thrombophilia (antibody work up)
Algorithm for diagnosis is given in figure.1.

**Management**

Leg elevation and compression stockings and physiotherapy is needed. Warfarin should be avoided in first trimester due to teratogenicity. Fondoparinux is avoided due to paucity of safety data in pregnancy. The only potential indication is the setting of heparin induced thrombocytopenia. Safety of direct oral anticoagulants also needs validation and is not used. Vigilance is needs as an appropriate dose of anticoagulants in pregnancy is also not validated thoroughly as of now. When indicated initiation should be with subcutaneous low molecular weight heparin (LMWH), Intravenous unfractionated heparin (IV UFH) or s/c UFH. LMWH has a better safety profile and greater reduction in thrombus size. Intravenous UFH is preferred in patients with pulmonary embolism or persistent hypotension. Shorter half life and near complete reversal with protamine is possible. UFH (either IV or subcutaneous) is preferred over subcutaneous LMWH in patients who have severe renal failure.

LMWH
Heparin dosing is given in Table 4 and anticoagulant dosing in Table 5.
Dalteparin 200 units/kg once daily
Tinzaprin 175 units/kg once daily,
Dalteparin 100 units/kg every 12 hours
Enoxaparin 1 mg/kg every 12 hours

Titrate dose to achieve an anti-Xa level of 0.6 to 1.0 IU/mL for twice daily administration, or 1 to 2 IU/mL for once daily administration .Anti-Xa level is measured four hours after the third or fourth dose for twice daily dosing, or four hours after the second or third dose for daily dosing. Anti-Xa level is measured four hours after the third injection that follows a dose adjustment. Then recheck the level every one to three months. Some women require dose adjustments more frequently.

**IV UFH —**

IV UFH bolus of 80 units/kg, followed by a continuous infusion of 18 units/kg per hour (24).Infusion is titrated every six hours to achieve a therapeutic activated partial thromboplastin time (aPTT).aPTT should corresponds to an anti-Xa level of 0.3 to 0.7 U which is usually lab specific. Then it is rechecked once or twice daily. IV UFH can be transitioned to subcutaneous UFH or subcutaneous LMWH if long-term or outpatient anticoagulant therapy is planned.

**Labour and Delivery**

LMWH should be discontinued at least 24 hours prior to delivery if time is predictable and is important in those who desire neuraxial anaesthesia to avoid spinal hematoma. Those who are at high risk for recurrent VTE s/c LMWH or s/c UFH switch over to IV UFH and discontinue 4-6 hours prior to delivery. Neuraxial catheters should be placed only after aPTT returns to normal. Those with reduced cardiopulmonary reserve or pulmonary embolism may proceed to labour without discontinuation or placement of an IVC filter(25).For preterm delivery discontinue subcutaneous LMWH or UFH and use IV UFH instead. Heparin can be restarted 12 hrs after caesarean or 6 hours after vaginal birth when no significant bleeding has occurred. If Warfarin is chosen heparin and Warfarin overlap should be for at least 5 days. INR should be around 2-3 for 2 consecutive days when heparin can be discontinued. Warfarin does not accumulate in breast milk. Treatment should continue for 3-6 months in those with transient risk factors. Persistent risk factors need longer period of coverage with anticoagulants.

**IVC Filter**

These should be considered in those in whom anticoagulation is contraindicated, proven ineffective or in those who have developed complications of anticoagulation or in whom the pulmonary vascular bed can no longer tolerate another insult.

Thrombectomy and thrombolysis has been reserved for life threatening indications only. Maternal mortality of 1%, fetal loss of 6% and maternal haemorrhage of 8% is reported (26).

Antiphospholipid antibody syndrome warrants treatment with heparin and aspirin (75-100mg).

Surgical pulmonary embolectomy is indicated for patients who are diagnosed with sub massive and/or massive acute pulmonary emboli, thrombus-in-transit, concomitant cardiac pathology such as a large patent foramen ovale, or relative contraindications to thrombolytic therapy, including recent cerebrovascular or intracranial pathology, recent surgery, active bleeding, or other absolute contraindications to anticoagulation. Currently modified minimally invasive approached with thoracoscopic assistance can also be done in specialist centres. Many advanced centres have PERT pulmonary emergency response team which can be alerted. Surgical embolectomy rather than percutaneous catheter thrombectomy should be considered in the presence of free-floating cardiac thrombi or in patients with paradoxical embolism from a large atrial septal defect. Accepted indications for catheter directed embolectomy include :1) hemodynamic instability, defined as a systolic blood pressure (SBP) 40 mmHg, or ongoing administration of catecholamines for treatment of systemic arterial hypotension; 2) subtotal or total embolic occlusion of the left and/or right main pulmonary artery by chest CT or by conventional pulmonary angiography; 3) echocardiographic findings indicating right ventricular after load stress with or without pulmonary hypertension; and 4) clinically severe acute PE with a contraindication to anticoagulation or systemic thrombolytic therapy.

## CONCLUSION

Initial diagnosis depends on good degree of clinical suspicion with supportive investigations to diagnose the condition. Therapy should be continued at least 6 weeks postpartum and a total duration of 3- 6 months treatment is warranted. Table 6 gives the list and duration of treatment according to risk. Longer duration of treatment is required in those with persistent risk factors. Heparin still is the mainstay of treatment in pregnancy and peurperium. Heparin is only considered in first trimester and Warfarin can be started from 13 weeks.

**Table 1 Risk factors - venous thromboembolism in pregnancy.**

| | |
|---|---|
| **General** | Activation of Virchow's triad, venous stasis from obstruction to flow, hypercoagulability, endothelial damage |
| | Inherited thrombophilia, previous venous thromboembolism |
| **Antepartum** | Multiple births |
| | Varicose veins |
| | Inflammatory bowel disease |
| | Urinary tract infection |
| | Diabetes |
| | Hospitalization for non-delivery reasons (particularly those >3 days) |
| | BMI ≥30 kg/m$^2$ |
| | Increased maternal age ≥35 years |
| **Postpartum** | Cesarean section |
| | Medical comorbidities (eg, varicose veins, cardiac disease, inflammatory bowel disease) |
| | BMI ≥25 kg/m$^2$ |
| | Young gestational age (preterm delivery <36 weeks) |
| | Obstetric hemorrhage |
| | Stillbirth |
| | Increased maternal age ≥35 years |
| | Hypertension |

**Table 2 Inherited Thrombophilias**

Congenital
1. Factor V Leiden ( 4 times more risk)
2. Antithrombin III ( 8 fold risk)
3. Protein S, or protein C deficiency ( 8 fold risk)
4. Antiphospholipid syndrome ( 5% risk)

Acquired
Antiphospholipid syndrome

**Table 3 Signs and symptoms of DVT in pregnancy**

| Signs and Symptoms |
|---|
| • Dyspnea |
| • Palpitations |
| • Pleuritic chest pain |
| • Hemoptysis |
| • Cyanosis/hypoxia in massive PE |
| • Tachycardia |
| • Tachypnea |
| • Hypotension |
| • Collapse |
| • +/- symptoms or signs of DVT |
| • DVT in pregnancy usually proximal |
| • Unilateral leg pain/tenderness |
| • Swelling in an extremity |
| • Increase calf/thigh circumference |
| • Increased temperature |
| • Prominent superficial veins |
| • Pitting edema |

**Table 4 Heparin and dosing**

| Heparin | |
|---|---|
| Types | I. Unfractionated heparin → UFH "Cal-heparin"<br>II. Low molecular weight heparin → LMWH "Clexan" |
| Onset | Within 10 minutes |
| Half-life | 6 hours |
| Doses | I. Unfractionated heparin<br>• Normal body weight → 5000 IU/day<br>• Body weight < 50 kg → 2500 IU/day<br>• Body weight > 90 kg → 5000 IU/12 h<br>• High prophylactic dose→ 100 IU/kg/12h<br>II. Low molecular weight heparin<br>• Normal body weight → 40 mg/day<br>• Body weight < 50 kg → 20 mg /day<br>• Body weight > 90 kg → 40 mg / 12h<br>• High prophylactic dose→ 1 mg/kg/12h |
| Monitoring | 1. Activated partial thromboplastin aPPT twice weekly<br>2. Plattlets concentration monthly<br>3. Bone mineral density every 3 months |
| Advantages | 1. No effect on the fetus ( does not cross placental blood barrier )<br>2. Not secreted on milk ( no effect on lactation )<br>N.B : advantages of LMWH over UFH<br>o Fewer side effect<br>o Prolonged half-life<br>o Greater inhibitory effect on factor X<br>o Prophylactic dose once daily<br>o No need for continuous laboratory monitoring |
| Drawbacks | • Increase bleeding tendency |

**Table 5 Anticoagulant dosing**

| | |
|---|---|
| Types | I. Coumarine → Warfarin sodium "Marevan"<br>II. Indandione → phenoidione "Dindevan" |
| Onset | Full effect after 5 days |
| Half-life | • Warfarin → 44 hours<br>• Phenoidione → 5 hours |
| Doses | 2 to 5 mg/day |
| Monitoring | 1. INR = " international randomized ratio "→ should be 2 to 3<br>2. PT = " prothrombine time "→ 30–50 % of normal control |
| Advantages | Oral route , potent and long acting |
| Drawbacks | • Maternal :<br>1. Skin: allergy, fever, rash, urticarial and dermatitis<br>2. Blood: agranulocytosis<br>3. Liver: liver disturbances; jaundice<br>4. Renal: renal disturbances; hematuria<br>5. Over dose → bleeding tendency<br>• Fetal :<br>1. Warfarin embryopathy; nasal hypoplasia, depression of nasal bone, mental retardation, optic atrophy, skeletal defect ' bone splitting'<br>2. Can cross placental-blood barrier; bleeding tendency and increases the risks of intracranial hemorrhage and accidental hemorrhage<br>• Drug interactions :<br>1. drugs increases the effect : salicylates, quinine, steroids<br>2. drugs decreases the effect : hepatic enzyme inducers |
| Anti-dot | • Vitamin K IM. , SC.<br>• For rapid effect :<br>1. Fresh blood , fresh frozen plasma<br>2. Vitamin K to the mother and baby |

**Table 6 Risk Group Analysis and duration of treatment**

| | |
|---|---|
| **Very high risk** | |
| Criteria | • Previous VTE with thrombophilia<br>• Long term warfarin therapy |
| Antepartum | • High prophylactic dose or therapeutic dose of LMWH |
| Postpartum | • LMWH for 5 days + Warfarin |
| **High risk** | |
| Criteria | • Previous recurrent VTE<br>• VTE once with thrombophilia<br>• VTE once with positive family history<br>• Diagnosed important thrombophilia<br>• Valvular mechanical prosthesis |
| Antepartum | • prophylactic dose LMWH |
| Postpartum | • LMWH for 5 days + Warfarin for 6 weeks |
| **Moderate risk** | |
| Criteria | • Single provoked VTE without thrombophilia<br>• Thrombophilia + Anti-thrombin III deficiency<br>• Mitral stenosis |
| Antepartum | • Antenatal aspirin |
| Postpartum | • LMWH for 5 days + Warfarin for 6 weeks |
| **Low risk** | |
| Criteria | Two or more of the following :<br>• Obesity<br>• Age > 35<br>• Parity > 4<br>• Gross varicose veins<br>• Recurrent hypertensive disorders |
| Antepartum | • Antenatal aspirin |
| Postpartum | • Warfarin for 6 weeks |

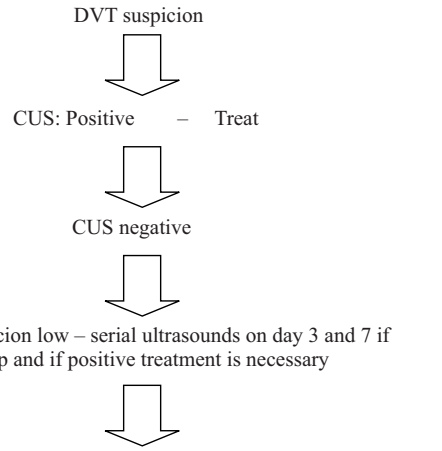


**Figure - 1. Management Algorithm for DVT suspicion in pregnancy**

## REFERENCES


1. Kujovich JL. Hormones and pregnancy: thromboembolic risks for women. Br J Haematology 2004; 126:443.
2. Heit JA, Kobbervig CE, James AH, et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005; 143:697.
3. Morris JM, Algert CS, Roberts CL. Incidence and risk factors for pulmonary embolism in the postpartum period. J Thromb Haemost 2010; 8:998.
4. James AH, Jamison MG, Brancazio LR, Myers ER. Venous thromboembolism during pregnancy and the postpartum period: incidence, risk factors, and mortality. Am J Obstet Gynecol 2006; 194:1311?
5. The National Institute for Clinical Excellence. Why mothers die 2000–2002 — report on confidential enquiries into maternal deaths in the United Kingdom. London: Royal College of Obstetricians and Gynaecologists Press, 2003.
6. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving mothers' lives: reviewing maternal deaths to make motherhood safer — 2003–2005: the seventh report on confidential enquiries into maternal deaths in the United Kingdom. London: CEMACH, 2007.
7. Sultan AA, West J, Grainge MJ, et al. Development and validation of risk prediction model for venous thromboembolism in postpartum women: multinational cohort study. BMJ 2016; 355:i6253.
8. Heit JA, Kobbervig CE, James AH, et al. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. Ann Intern Med 2005; 143:697.
9. McColl MD, Ramsay JE, Tait RC, et al. Risk factors for pregnancy associated venous thromboembolism. Thromb Haemost 1997; 78:1183.
10. Blondon M, Harrington LB, Righini M, et al. Racial and ethnic differences in the risk of postpartum venous thromboembolism: a population-based, case-control study. J Thromb Haemost 2014; 12:2002.
11. Ghaji N, Boulet SL, Tepper N, Hooper WC. Trends in venous thromboembolism among pregnancy-related hospitalizations, United States, 1994-2009. Am J Obstet Gynecol 2013; 209:433.e1.
12. Kujovich JL. Hormones and pregnancy: thromboembolic risks for women. Br J Haematology 2004; 126:443.
13. Gherman RB, Goodwin TM, Leung B, et al. Incidence, clinical characteristics, and timing of objectively diagnosed venous thromboembolism during pregnancy. Obstet Gynecol 1999; 94:730.
14. Kamel H, Navi BB, Sriram N, et al. Risk of a thrombotic event after the 6-week postpartum period. N Engl J Med 2014; 370:1307.
15. Tepper NK, Boulet SL, Whiteman MK, et al. Postpartum venous thromboembolism: incidence and risk factors. Obstet Gynecol 2014; 123:987.
16. Abdul Sultan A, Grainge MJ, West J, et al. Impact of risk factors on the timing of first postpartum venous thromboembolism: a population-based cohort study from England. Blood 2014; 124:2872.
17. Bergrem A, Dahm AE, Jacobsen AF, et al. Differential haemostatic risk factors for pregnancy-related deep-vein thrombosis and pulmonary embolism: a population-based case-control study. Thromb Haemost 2012; 108:1165.
18. Zotz RB, Gerhardt A, Scharf RE. Inherited thrombophilia and gestational venous thromboembolism. Best Pract Res Clin Haematol 2003; 16:243.
19. Goodrich S M, Wood J E. Peripheral Venous Distensibility and Velocity of Venous blood flow during pregnancy or oral contraceptive therapy. Am J Obstet Gynecol 1964; 90:740.
20. Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. N Engl J Med 2008; 359:2025.
21. Gerbasi FR, Bottoms S, Farag A, Mammen E. Increased intravascular coagulation associated with pregnancy. Obstet Gynecol 1990; 75:385.
22. Chan WS, Lee A, Spencer FA, et al. D- Dimer testing in pregnant patients: towards determining the next 'level' in the diagnosis of deep vein thrombosis. J Thromb Haemost 2010; 8:1004.
23. Bates SM, Greer IA, Middeldorp S, et al. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed : American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141:e691S.
24. Hirsh J, Bauer KA, Donati MB, et al. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133:141S.
25. Dulitzki M, Pauzner R, Langevitz P, et al. Low-molecular-weight heparin during pregnancy and delivery: preliminary experience with 41 pregnancies. Obstet Gynecol 1996; 87:380.
26. Turrentine MA, Braems G, Ramirez MM. Use of thrombolytics for the treatment of thromboembolic disease during pregnancy. Obstet Gynecol Surv 1995; 50:534.
27. Fallon J, Zapata D, Pickens A, Halkos M, Lattouf O. Minimally Invasive Pulmonary Embolectomy With Thoracoscopic Assistance-March 2020. doi: 10. 25373/ ctsnet. 11964948