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Thromboembolic Diseases in Pregnancy

VINAY GOEL, VINEETA TANEJA, SANJAY GOGIA, SANJAY DHALL

INTRODUCTION

Risk of venous thromboembolism in pregnancy is approximately six times greater than in non-pregnant state. Symptoms of thrombophlebitis or their absence do not accurately predict the diagnosis, disease severity, or risk of embolization. Thromboembolic disorders can occur without symptoms, with only minimal symptoms, or with significant symptoms. Also, calf edema, cramping, and tenderness, which may occur normally during pregnancy, may simulate Homans' sign. It is important thereby to make a definitive diagnosis, to ensure correct treatment and because of the implications for subsequent pregnancies.

Pathophysiology

This increased risk for thromboembolic disease is mainly due to venous stasis in legs and physiological changes in several coagulation factors during pregnancy (Fig. 1). These include:

a. Resistance to activated protein C increases in second and third trimester
b. Protein S activity decreases due to estrogen induced decreases in total protein S and complement 4b binding protein which binds protein S
c. Fibrinogen and factors II, VII, VIII and X increase
d. Activity of fibrinolytic inhibitors, thrombin activatable fibrinolytic inhibitor TAFI and PAI–2 increases.

CLINICAL MANIFESTATIONS

Maternal

The net effect of prothrombin changes in pregnancy have been associated with poor maternal outcomes, predisposing women to deep vein thrombosis and pulmonary embolism. Overall risk of DVT in pregnancy (0.5-1.8%) is higher in women with previous VTE and has recurrence rate of 1 in 71 women. Maternal DVT is more common in left leg (accounting for 85 percent of leg thrombosis, occurs more commonly in ileo femoral veins than in calf veins and is more often associated with pulmonary embolism[1]. The occurrence of thrombotic events during pregnancy is also affected by presence of other risk factors such as operative delivery, age over 35 years, high parity, high body mass index, previous use of oral contraceptive pills, smoking.

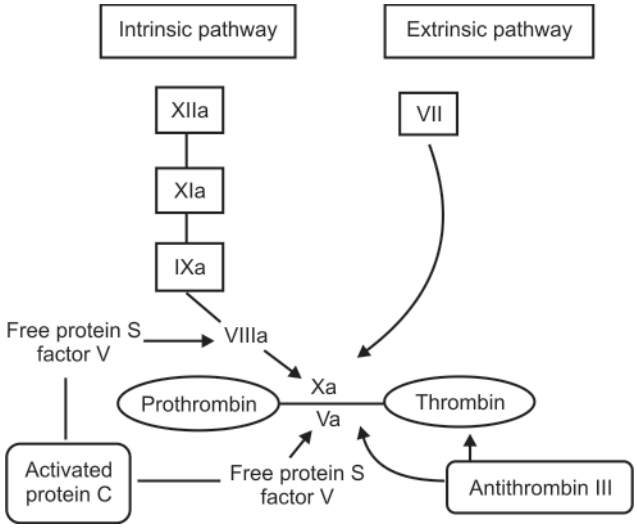

Fig. 1: Coagulation cascade

Pulmonary embolism usually occurs during third trimester or postpartum. Pulmonary embolism occurs in approximately 16% of untreated DVT patients diagnosis during pregnancy is difficult due to overlapping symptoms and elevation of D - dimers may be unrelated to VTE.

An increased cerebrovascular ischemic events during pregnancy have also been associated with pregnancy related hypertension, eclmapsia and maternal age[2,3].

FETAL

Hemostatic system plays an important role in normal development of fetus. Prothrombotic changes and thrombosis in placenta may interfere with normal pregnancy. Intervillous or spiral artery thrombosis, Decidual Vasculopathy, Intervillous fibrin deposition and inadequate placental perfusion leads to a myriad of fetal and obstetrical complications including: Still birth, severe intrauterine growth retardation (IUGR), placental abruption, severe and early onset pre-eclampsia[4]. Further, thrombophilic states have been associated with development of severe pre-eclampsia only and not in mild pre-eclampsia. These complications have high recurrence rates in subsequent pregnancies, while the type of complications may change from one pregnancy to other, e.g. severe pre-eclampsia to IUGR.

TYPES OF THROMBOPHILIAS

Acquired Thrombophilia

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS), an acquired autoimmune condition is characterized by presence of lupus anticoagulant (LAC) and/or anticardolipin antibodies (aCL) with thrombosis (both arterial and venous), recurrent fetal loss in second and third trimester and autoimmune thrombocytopenia[5].

This condition is associated with placental vascular thrombosis, and in turn may result in miscarriage, IUGR, still birth and early severe pre-eclampsia.

Inherited Thrombophilia

Many inherited conditions have been associated with thromboembolic events in patients with otherwise no apparent risk for thrombosis (Table 1).

a. Resistance to activated protein C (Factor V Leiden) is the most common of inherited thrombophilia and is inherited as autosomal dominant pattern.
b. Prothrombin gene mutation at nucleotide 20210 leads to increase prothrombin levels and hypercoagulable state with increased risk of cerebral vein thrombosis[6].
c. Abnormalities of methionine metabolism leads to hyperhomocysteinemia, which in turn causes direct endothelial injury.
d. Protien C, protein S and antithrombin III deficiency are other less common causes of autosomal dominant coagulopathies (Table 2).

Table 1: Prevalence of inherited thrombophilias

	General population	*Patients with VTE*
Factor V Leiden	5%	25%
Prothrombin gene mutation	2%	6%
Hyperhomocysteinemia	3%	10%
Protein C, S and anti-thrombin deficiency	<1%	10%

DIAGNOSIS

Most maternal thromboembolic complications develop 6- 8 weeks postpartum and result from vascular trauma during delivery.

Diagnosis usually requires clinical awareness and anticoagulants may be initiated on strong clinical suspicion only, but in view of potential hazards, an objective diagnosis is mandatory.

Doppler ultrasonography is primary investigation for suspected deep vein thrombosis. Elevation of D dimmers in pregnancy may be unrelated to VTE.

If pulmonary embolism is suspected, a lung ventilation and perfusion scan may be performed to confirm the diagnosis. The procedure is safe during pregnancy because the dose of the radioactive substance is so small. If the diagnosis of pulmonary embolism is still uncertain, pulmonary angiography is required.

Screening for thrombophilia is recommended for high risk group women:

1. History of VTE < 45 years
2. Unusual manifestations of thromboembolism including focal neurological deficits
3. Strong family history of VTE
4. Recurrent fetal loss,
5. Still birth, IUFD, IUGR, abruptio placenta
6. Severe or recurrent pre-eclampsia.

It is important to note that not all women with Thrombophilia will develop VTE during pregnancy suggesting existence of, yet unidentified, environmental factors.

TREATMENT

With current management strategies, using unfractionated or low-molecular-weight heparin (LMWH) and

Table 2: Association of pregnancy complications and thrombophilia

	Severe pre-eclampsia	*IUGR*	*Placental Abruption*	*Fetal Loss*
Antiphospholipid syndrome	++	++	++	++
Factor V leiden	++		++	++
Protein C, S deficiency	++	++		++
Hyperhomocysteinemia			+	
Antithrombin deficiency	++	++	+	

aspirin, a greater than 70% live birth rate may be achieved in affected pregnancies (Table 3). A multidisciplinary approach in the management of these women should focus for primary thromboprophylaxis in asymtomatic women, secondary thromboprophylaxis in women who have previously developed VTE and treatment of acute thrombotic episodes.

Heparin (Unfractionated/LMWH) are the drugs of choice for prevention and treatment of VTE[7]. Heparin does not cross the placenta and causes no harm to fetus. However, altered metabolism of heparin during pregnancy requires frequent monitoring of aPTT or measurements of anti factor Xa concentrations 3-6 hours after the injection as guide to final dose specially if used for therapeutic purpose. Dose of heparin should be reduced during delivery and spinal anesthesia should be delayed by at least 6-12 hours after last dose. Heparin may be restarted 02 hours after delivery.

Oral anticoagulants (OAC) are rarely used during pregnancy as these drugs cross the placenta and are known to produce embryopathy in 4-5% of expose fetus, especially during first trimester. Nervous system anomalies can occur on exposure in any trimester[8]. OACs are mainly indicated for management of women with artificial heart valves[9]. This drugs are also indicated for women having heparin induced thrombocytopenia, skin allergy.

Heparin, LMWH and oral anticoagulants are not secreted in breast milk and can be safely given to nursing mothers.

Aspirin (0.1 g per day) alongwith heparin is indicated for women with antiphospholipid syndrome and previous thrombotic episodes. Women who develop neurological deficits during pregnancy should be treated with high dose 0.3-0.5 g per day[10].

Treatment of Acute Thrombotic Episode

Acute DVT during pregnancy with or without thrombophilia has to be treated with full dose of intravenous heparin for 5-10 days followed by maintainance subcutaneous heparin given twice daily adjusted as per aPTT monitoring.

Summary

Thromboembolism in pregnancy is fairly common problem with many maternal and fetal complications. Approach to these disorders requires clinical prediction and work up for acquired or inherited thrombophilias. However, outcome of pregnancy may be improved with appropriate risk stratification and timely administration of heparin and /or aspirin.

Table 3: Treatment Recommendations

Category	*Patients*	*Recommendations*	*Duration*
Very high risk	— Previous VTE — VTE in current pregnancy — Antithrombin deficiency	LMWH twice daily OR heparin adjusted dose — OACs to be started postpartum	Throughout pregnancy till 6-12 weeks postpartum
High risk	— Homozygote FV — Thrombophilia plus Family history of VTE — Combined thrombophilia	LMWH once daily OR Fixed dose heparin — OACs to be stared postpartum	Throughout pregnancy till 6-12 weeks postpartum
Moderate risk	— Heterozygote FV — Prothrombin mutation, Protein C, S deficiency — Family History of VTE	— Postpartum anticoagulation LMWH once daily	6-12 weeks postpartum
Low risk	— Heterozygote FV, prothrombin mutation, no personal or family history of VTE	Monitor for additional risk factors	

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