Prevention and Treatment of Venous Thromboembolism (VTE) in Obstetrics

These guidelines have been reviewed and approved by the Maternal Fetal Medicine Committee and were approved by the Council of the SOGC.

Abstract

Objective: to identify risk factors for venous thromboembolism (VTE) in the peripartum period and to provide guidelines for risk assessment and thromboprophylactic measures for VTE in pregnant women. Guidelines for diagnostic testing and for acute and long term treatment of VTE are also provided.

Options: specific subgroups of pregnant women are defined and appropriate prophylactic measures are outlined.

Outcomes: venous thromboembolism remains a major cause of morbidity and mortality in pregnancy and the postpartum period. Identification of risk and adequate prophylaxis can decrease the incidence of VTE.

Evidence: evidence was gathered using Medline (National Library of Medicine) to identify relevant studies and from bibliographies of articles thus identified.

Recommendations: although evidence is lacking to date from Grade I studies (properly controlled randomized studies) in pregnant patients, there is good evidence to support the role of prophylaxis in reducing the incidence of VTE in patients identified to be at risk in the non-pregnant population (II B). Based on risk assessment more patients should be considered for thromboprophylaxis, including women with a past history of a VTE and a known thrombophilia on long-term anticoagulation, women with a past history of a VTE, women with a known thrombophilia who have never experienced a VTE and potentially considered in women at the time of Caesarean section (II B; III C). The occurrence of VTE is effectively reduced by the use of low dose unfractionated heparin. Experience with low molecular weight heparin and pregnancy is building, but is limited at present. Unfractionated heparin remains the standard for the treatment of VTE in pregnancy at the present time. Following initial heparinization for the treatment of VTE, patients should be continued on anticoagulation throughout pregnancy and for six to 12 weeks postpartum or a total of three months of anticoagulation (II A).

INTRODUCTION

Venous thromboembolism (VTE) is a major cause of maternal morbidity and mortality. The incidence has been reported to range from 0.5-3/1,000 pregnancies occurring with approximately equal frequency in all three trimesters and postpartum. Several risk factors predispose the pregnant patient to the development of VTE. Once VTE has occurred, prompt and adequate treatment must be initiated in order to reduce the morbidity and mortality associated with pulmonary embolism (PE), to reduce the extension of a deep vein thrombosis (DVT), and to reduce the morbidity associated with post-thrombotic leg syndrome.

In a woman with a previous history of VTE the recurrence risk can be as high as 12 percent. Thromboprophylaxis is more effective than treatment of established disease in decreasing the
associated morbidity and mortality. The purpose of this paper is to provide guidelines for risk assessment, prophylaxis, diagnosis and treatment of VTE in pregnancy.

**RISK FACTORS**

A number of risk factors for the development of thromboembolic disease in pregnancy have been identified. Risk factors associated with uncomplicated pregnancy are summarized in Table I.

Risk factors that may be present in addition to those inherent in the pregnant state are listed in Table II. Thrombophilia is the term used to describe familial (congenital) or acquired abnormalities of hemostasis that could predispose an individual to venous thromboembolism. The main congenital thrombophilias are listed in Table II. It is possible for a woman to have more than one thrombophilia, as congenital thrombophilia may be a multigene disorder. Increased thrombosis is also associated with acquired thrombophilias, such as the antiphospholipid antibody syndrome (APA).

Congenital and acquired factors are often present concurrently. The risk of VTE increases with multiple factors.

It should be noted that women with APA syndrome and hyperhomocysteinemia are at increased risk of both venous and arterial thrombosis, hence management in these women should include daily low dose aspirin.

Most women with thrombophilias remain asymptomatic. However, thrombophilia screening should be offered to any woman with a personal or family history of a VTE, especially if the VTE occurred in the absence of other recognized risk factors or outside the pelvis and lower limbs in the context of a pregnancy. There is growing evidence to suggest that the incidence of thrombophilias is also increased in women with pregnancy complications, including late fetal loss, gestational hypertension, and intrauterine growth restriction. It is reasonable to consider thrombophilia screening in women with a history of one or more of the above poor outcomes.

Although factors have been identified which increase the risk of VTE in pregnancy, it should be noted that most such events occur in the absence of such features. The prudent physician should have high suspicion for thromboembolic disease when suggestive symptoms and signs are present, and investigate the possibility thoroughly regardless of whether risk factors are present.

**THROMBOPROPHYLAXIS IN OBSTETRICS**

The issue of thromboprophylaxis is controversial. Expert opinion varies as to when, in whom, and how to use prophylaxis against VTE. The degree of anticoagulation depends on the particular thrombophilia involved and the specific risk factors present in any given case.

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>PREDISPOSING RISK FACTORS ASSOCIATED WITH PREGNANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYPERCOAGULABILITY</strong></td>
<td><strong>STASIS</strong></td>
</tr>
<tr>
<td>Increased factors; II, V, VII, VIII, IX, X, XII and fibrinogen</td>
<td>Increased venous distensibility, decreased venous tone</td>
</tr>
<tr>
<td>Increased platelet aggregation</td>
<td>50% decrease in venous flow in lower extremity by third trimester</td>
</tr>
<tr>
<td>Decreased protein S, tissue plasminogen activator, factors XI, XIII</td>
<td>Uterus is mechanical impediment to venous return</td>
</tr>
<tr>
<td>Increased resistance to activated protein C</td>
<td></td>
</tr>
<tr>
<td>Antithrombin can be normal or reduced</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE II</th>
<th>ADDITIONAL RISK FACTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous VTE</td>
<td>Thrombophilias*</td>
</tr>
<tr>
<td>Age &gt; 35</td>
<td>Congenital - protein C &amp; protein S deficiencies</td>
</tr>
<tr>
<td>Obesity</td>
<td>resistance to activated protein C (Factor V Leiden)</td>
</tr>
<tr>
<td>Infection</td>
<td>antithrombin deficiency</td>
</tr>
<tr>
<td>Bedrest/physical immobility</td>
<td>hyperhomocysteinemia</td>
</tr>
<tr>
<td>Shock/dehydration</td>
<td>prothrombin gene variant</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>plasminogen deficiency</td>
</tr>
<tr>
<td>Operative vaginal delivery</td>
<td>Acquired - antiphospholipid antibody syndrome</td>
</tr>
<tr>
<td>Uterine instrumentation</td>
<td>nephrotic syndrome (decreased antithrombin levels)</td>
</tr>
<tr>
<td>Pelvic surgery in the peripartum period</td>
<td></td>
</tr>
</tbody>
</table>

* The field of thrombophilias is in evolution. Additional thrombophilias are being discovered.
a) Women with a past history of VTE and known thrombophilia, on long-term anticoagulation

Full therapeutic anticoagulation is recommended throughout pregnancy and for 6-12 weeks postpartum, after which the previous anticoagulation regimen is resumed. For suggested regimens see below in “Treatment of VTE Occurring in Pregnancy: Long-term Treatment.” Management may be modified based on the specific thrombophilia involved. (III B)

b) Women with a past history of VTE

The recurrence risk may be as high as 12 percent. Yet there remains disagreement as to whether thromboprophylaxis in these cases is necessary or not. There is a lack of prospective trials on the effect of prophylaxis to prevent the recurrence of VTE in pregnancy. However, based upon trials in the non-pregnant population, the recommendation is to use one of the following regimens in a patient with a previous VTE and institute anticoagulation postpartum for six weeks. (II B)

Prophylactic regimens:
- Unfractionated heparin 5,000 units sc every 12 hours throughout pregnancy. (I B)
- Unfractionated heparin 5,000 units sc every 12 hours in the first trimester, 7,500 units every 12 hours in the second trimester, and 10,000 units every 12 hours in the third trimester. (I B)

The second regimen is recommended based on the higher heparin dosages needed to achieve adequate heparin levels as pregnancy advances.

- Low molecular weight heparin (LMWH):
  - Dalteparin (Fragmin®) - 2,500 IU sc if < 50 kg, 5,000 IU sc if 50-70 kg, 7,500 IU sc if > 71 kg once a day
  - Enoxaparin - 40 mg sc once a day

There is insufficient evidence in pregnancy with respect to the use of LMWH to recommend its use routinely at present. In cases where the previous VTE was unrelated to pregnancy or exogenous hormonal use, one further option remains to monitor with clinical surveillance throughout pregnancy and institute anticoagulation postpartum for six weeks.

c) Women with a known thrombophilia who have never experienced a VTE

The management in these cases is even more controversial. There is a lack of any prospective evidence to demonstrate that these women benefit from thromboprophylaxis. In addition, management needs to be determined by the thrombophilia involved, as the risk of a VTE varies with the specific condition. For example, the significant risk of VTE with a known antithrombin deficiency (50-70%) is present throughout pregnancy. Anticoagulant prophylaxis should be instituted once the pregnancy is confirmed and continued postpartum. Similar management is recommended with cases in which there are multiple thrombophilias, as the risk for DVT is considered to be higher. However, with protein C and S deficiencies the risk of VTE is greatest in the postpartum period (18-20%). Hence, it may be acceptable to delay anticoagulant prophylaxis until labour and delivery and continue it for 12 weeks postpartum. (III C)

Current prophylaxis regimens for acquired thrombophilias, such as APA syndrome, include the use of low dose aspirin in conjunction with prophylactic heparin. (I B)

Women in this category should be referred to a centre familiar with these disorders for individualized management. Recommendation for thromboprophylaxis or full therapeutic treatment is based on Grade III C evidence. (I B)

d) Consideration of postpartum thromboprophylaxis following Caesarean section

No prospective studies exist to evaluate the effectiveness of thromboprophylaxis following a Caesarean section to prevent VTE. The Royal College of Obstetricians and Gynaecologists in Britain has issued a report recommending the use of postpartum thromboprophylaxis in women who have moderate to high risk for VTE in association with a Caesarean section. Prophylaxis needs to be considered in the presence of risk factors such as a previous VTE, a known thrombophilia (II B), a history of prolonged immobility or obesity. (III C) It is recommended to start treatment following delivery of the neonate at the time of the Caesarean section.

- Unfractionated heparin 5,000 units sc every 12 hours until fully mobile
- LMWH sc once a day for five days, such as Enoxaparin 20 mg sc od

SIDE EFFECTS AND COMPLICATIONS OF HEPARIN THERAPY

Heparin-induced thrombocytopenia (HIT), caused by heparin-dependent IgG antibodies, is an uncommon (3%) but serious complication typically occurring six to 12 days after initiation of therapy. If a patient has previously had heparin therapy the thrombocytopenia may occur more rapidly. The risk of major bleeding episodes is low (2-10%), however minor to moderate bleeding is increased slightly with unfractionated heparin. Bruising at injection sites is common and can be decreased by instruction in appropriate injection technique. Osteoporosis is a dose dependent complication related to the duration of therapy.

Allergies are uncommon to unfractionated heparin. Anticoagulation for a woman unable to take heparin, for whatever reason, should be managed by a haematologist.

LOW MOLECULAR WEIGHT HEPARIN

Experience with low molecular weight heparin (LMWH) in obstetrics is limited. LMWH may be administered once or twice a day. Dosage is based on maternal weight and requires less
monitoring as it has a predictable anticoagulant effect. LMWH does not cross the placenta\cite{14} and does not appear to have teratogenic effects in animal studies.\cite{13} Bleeding appears to be less with LMWH\cite{16} although this remains to be confirmed in large trials. The risk of thrombocytopenia is less than with unfractionated heparin\cite{17} and the risk of osteoporosis may also be less.\cite{13} Cost remains a concern, as low molecular weight heparin is expensive at present. Large clinical trials using LMWH in pregnancy remain to be done. However, research is in progress.

At the present time unfractionated heparin remains the standard of care for anticoagulation in pregnancy in North America. There is insufficient evidence to date to suggest that LMWH is superior to unfractionated heparin in the prophylaxis and treatment of VTE in obstetrics.

**WARFARIN**

Warfarin is contraindicated during pregnancy due to its potential fetal effects. In the first trimester there is a risk of warfarin embryopathy (nasal hypoplasia, stippled epiphyses, eye anomalies, and developmental delay). Central nervous system abnormalities can occur at any stage in pregnancy. In addition there is a risk of fetal and neonatal hemorrhage with warfarin usage, especially near term.

**DIAGNOSIS OF VTE**

**DIAGNOSIS OF A DVT**

A high index of suspicion for DVT should be maintained. Most occur in the iliofemoral or calf veins with a predilection for the left leg (90%). Clinical and objective diagnosis is mandatory. Non-invasive diagnosis is recommended whenever feasible.

For DVT, venography is the gold standard. This invasive test involves radiation to both mother and fetus. A limited venogram, using lead apron shielding over the maternal abdomen and pelvis, decreases the radiation exposure to the fetus to <0.05 rads but visualization of the iliac veins is compromised. A limited venogram is sufficient if possible.\cite{18}

Serial impedance plethysmography (IPG) measures the changes in electrical impedance as the result of changes in blood volume within the limb. It can rule out a DVT when performed serially, but sensitivity and specificity are compromised late in pregnancy due to compression of the iliac veins.\cite{19}

In the non-pregnant patient Duplex Doppler sonography has a 95 percent correlation with venography for popliteal and femoral vein thromboses. The thrombus itself can be seen in the occluded segment of the vessel, enhanced by the use of external compression. Internal compression by the gravid uterus, however, limits its sensitivity and specificity in pregnancy.\cite{20}

Prospective studies looking at the sensitivity and specificity of Duplex Doppler to detect a DVT in pregnancy, along with those assessing the safety of withholding anticoagulants in pregnant patients with serial negative Duplex Doppler studies, are lacking.\cite{20} However, it is a simple non-invasive test and in many centres is the initial test in a pregnant women with a suspected DVT.

Both Duplex Doppler and IPG have poor sensitivity to detect a calf vein DVT. It is necessary to repeat testing in those with a negative scan and a high clinical suspicion. Therapy may be safely withheld if serial studies are negative.\cite{19} Venography should be performed if non-invasive studies are equivocal or unavailable.

Radioactive iodine labeled fibrinogen scanning is contraindicated in pregnancy. A single noninvasive study showing thrombosis or a positive venogram justifies treatment with anticoagulation.

**DIAGNOSIS OF A PE**

The symptoms and signs of a PE, as in the non-pregnant patient, are non-specific. In view of the frequently vague clinical presentation and the potentially life-saving benefit of anticoagulation, early recourse to diagnostic testing is warranted whenever the diagnosis of a PE is entertained. Pulmonary angiography is the gold standard for the diagnosis of a PE but it is invasive and carries significant morbidity.\cite{21}

A chest X-ray and ventilation-perfusion scan (V/Q scan) are the primary tools for diagnosis. Radiation to the fetus with a V/Q scan is minimal. A PE can be ruled out in patients with a low clinical suspicion and a normal or low probability V/Q scan. The diagnosis of a PE can be made in patients with a high clinical suspicion and a high probability scan. The limitation of the test is in those patients with a suspected PE and an intermediate scan.\cite{22} It is reasonable to perform a Duplex Doppler or IPG to rule out a DVT in these cases. If these tests are normal, but the diagnosis is still a possibility, a pulmonary angiogram should be considered.

Given the significant implications of long-term treatment with anticoagulation and the impact on the use of hormonal therapy in the future, a suspicion of a VTE should be aggressively investigated with definitive studies unless contraindicated.

**TREATMENT OF VTE OCCURRING IN PREGNANCY**

The recommendation for treatment of a VTE in pregnancy is based on Grade II A evidence.

**INITIAL TREATMENT**

Before initiating treatment obtain a baseline CBC, including platelets (PT), and activated partial thromboplastin time (aPTT).

**Unfractionated heparin:**

Initial bolus of 5,000 IU followed by an infusion of approximately 30,000 IU/24 hours.

- Measure the aPTT six hours after the bolus.
- Adjust to keep the aPTT at the therapeutic level for the local centre (1.5 to 2.5 the control value).
- Repeat every 24 hours once therapeutic.
• Or measure the serum heparin level. Maintain serum heparin at 0.2-0.4 IU/ml (an aPTT of 60-85 sec).23
An example of a protocol for the adjustment of intravenous unfractionated heparin is listed in Table III.

LONG-TERM TREATMENT
1) Unfractionated heparin:
Adjust to keep aPTT at therapeutic levels six hours after the injection23 (1.5 to 2.5 times the control or a heparin level of 0.1-0.2 IU/ml).

2) Low molecular weight heparin:
For example, for a 50-70 kg woman:
• Tinzaparin – 175 IU/kg sc once per day
• Dalteparin – 200 IU/kg sc once per day
Dose chosen to achieve an antiXa heparin level of 0.3-0.75 four hours post-injection.
No regular monitoring is necessary, but a single antiXa level done in the third trimester will ensure that the dose administered is within the therapeutic range. Administration twice a day during pregnancy, especially in the third trimester, appears to achieve better therapeutic levels.

Therapy should be continued throughout pregnancy and for six to 12 weeks postpartum or for a total of three months of anticoagulation.5

INTRAPARTUM MANAGEMENT
If thromboprophylaxis is being used, the patient should be instructed to discontinue administration of sc heparin at the onset of regular uterine contractions or on the morning of a booked induction. If an elective Caesarean section is planned and thromboprophylaxis is being used, the last dose of heparin should be given 6-8 hours before the Caesarean section is to be performed.
Evidence is lacking to suggest the appropriate timing of the administration of LMWH close to delivery. Some centres decrease the dose of LMWH back to the first trimester levels at 38 weeks gestation.24 The half-life of LMWH is about four hours;25 hence each centre utilizing LMWH must decide their own protocol for administration close to delivery. If the patient is on a prophylactic regimen utilizing LMWH, it must be discontinued 24 hours before the day of induction of labour. If therapeutic regimen is required, the patient should be switched to subcutaneous heparin in the weeks before delivery as per the centre’s own protocol. The use of regional anesthesia must be individualized. The risk of a subdural haematoma should be low in the presence of normal coagulation studies or a heparin level <0.4 IU/ml.23

If therapeutic heparin is required throughout labour, the patient should be switched to intravenous heparin and the dose adjusted to a therapeutic aPTT. There is a slight increase in the incidence of haematomas in a vaginal tear or episiotomy, but postpartum haemorrhage is not increased. Regional anaesthesia is contraindicated with therapeutic heparin.26

If the aPTT is greater than the therapeutic level, protamine sulphate may be used to neutralize the heparin. One mg of protamine sulphate neutralizes 100 units of heparin. Do not give more than 50 mg over any 15 minute period intravenously.

POSTPARTUM MANAGEMENT
Heparin can be resumed 4-12 hours postpartum if required. The clinical picture, presence of risk factors, and the mode of delivery will modify management.

If ongoing anticoagulation is required, oral warfarin can be instituted after appropriate initial intravenous therapy with heparin, or sc heparin can be resumed.
The decision to continue with heparin or switch to oral warfarin postpartum is based on individual patient and physician preference. Both are safe for breast-feeding.

Warfarin may be started the day following delivery. It can be given as 7.5 mg/day po on day one and two. Adjust to keep the International Normalized Ratio (INR) in the therapeutic range of 2-3. Warfarin therapy should overlap with intravenous heparin for 4-5 days until the initial INR is greater than two on two consecutive days.

Experience with LMWH in the lactating woman is limited.

Thrombophilic screening should be offered to all women who experience a VTE during pregnancy in the absence of a known risk factor. This should be done at least 12

<p>| Table III TITRATION OF INTRAVENOUS UNFRACTIONATED HEPARIN23 (INFUSION OF 40 IU/ML OF HEPARIN) |
|---------------------------------|------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>aPTT (seconds)</th>
<th>Dosage change</th>
<th>Additional action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>Repeat bolus</td>
<td>Repeat aPTT in 6 hours</td>
</tr>
<tr>
<td>50-59</td>
<td>↑2,880 IU/24 hours iv</td>
<td>Repeat aPTT in 6 hours</td>
</tr>
<tr>
<td>60-85</td>
<td>Don't alter</td>
<td>Repeat aPTT the next morning</td>
</tr>
<tr>
<td>86-95</td>
<td>↓1,920 IU/24 hours iv</td>
<td>Repeat aPTT the next morning</td>
</tr>
<tr>
<td>96-120</td>
<td>Stop infusion for 30 minutes ↓1,920 IU/24 hours iv</td>
<td>Repeat aPTT in 6 hours</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>Stop infusion for 60 minutes ↓3,840 IU/24 hours iv</td>
<td>Repeat aPTT in 6 hours</td>
</tr>
</tbody>
</table>

It is essential to adequately anticoagulate the patient in the first 24 hours. Initial intravenous treatment should be maintained for 5-7 days.
weeks postpartum. Molecular screening for thrombophilias can be done during the pregnancy. However, functional tests, such as those required for antithrombin and protein C and S deficiencies, can be modified by the pregnant state. Hence, they should be repeated past the puerperium.

The long-term management of a woman with a confirmed thrombophilia should be referred to a centre with expertise in the management of these disorders.

NON-MEDICAL MANAGEMENT

• Compression stockings
  Reduce leg edema by raising legs and using graduated compression stockings (prescribe two; one to wash and one to wear). The stockings decrease the risk of post-thrombotic leg syndrome.3 There are no controlled trials of the use of compression stockings in pregnancy or postpartum. (III B)
  • Avoidance of prolonged sitting.
  Poor evidence to support a recommendation for or against its use. (III C)

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• Dr. Peter Tsang, consultant haematologist at Children & Women’s Health Centre, Vancouver, BC

REFERENCES


OTHER REFERENCES

The Thrombosis Interest Group. www.thrombosis interest group.