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# *Deep Vein Thrombosis and Pulmonary Embolism in Pregnancy: Diagnosis, Complications, and Management*

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**Abstract:** Venous thromboembolism is a leading cause for maternal mortality. Because of the increase risk for thromboembolism in pregnancy and the postpartum period, the clinician must be on high alert for the signs and symptoms and use appropriate diagnostics in a timely manner so that prompt anticoagulation therapy can be initiated. A diagnostic and management approach for both deep vein thrombosis and pulmonary embolism and for prophylaxis against thromboembolism in the obstetric patient are crucial to decreasing morbidity, mortality, and long-term sequelae.

**Key words:** thromboembolism, pregnancy, anticoagulation, thromboprophylaxis, thrombophilia obesity

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## *Introduction*

### DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Venous thromboembolic events have been a leading contributor to severe maternal morbidity and mortality in the United States for the past several decades.[1] This is in contrast to the developing world in which hemorrhage and complications from hypertensive disorders are the leading contributors to maternal death.[1] Fatal pulmonary embolism, although a rare complication of pregnancy, continues to be the leading cause of pregnancy-related mortality in Western Europe and the United States as other causes of maternal mortality (hemorrhage, sepsis) have declined.[1] Clearly, the increase in overweight

and obesity in pregnancy, as well as cesarean delivery, over the past several decades has had an impact on this increased risk for complications for venous thromboembolism. During pregnancy, the risk for venous thromboembolism is increased 4-fold over the nonpregnant state,[2,3] and during the postpartum period the risk increases to 20-fold over the nonpregnant state.[3]

To impact thromboembolism as a cause for maternal morbidity and mortality, the clinician must identify known factors that increase risk, have a high index of suspicion, use accurate and timely diagnostic modalities, therapeutic intervention, and preventive strategies for those deemed to be at high risk.

## PATHOGENESIS OF THROMBOEMBOLISM IN PREGNANCY

Pregnancy evokes a physiologically hypercoagulable state that has evolved as a protective mechanism from hemorrhage at the time of childbirth. Progressive changes in the coagulation and fibrinolytic systems occur to prepare for the major hemostatic challenge of delivery and placental separation. The hypercoagulable state of pregnancy is provoked by thrombin-mediated fibrin generation that increases throughout pregnancy. Pregnancy is associated with an increase in plasma concentration of coagulation factors and fibrinolysis inhibitors, changes in venous flow, and changes within blood vessel walls. Venous thrombi are intravascular deposits consisting predominantly of fibrin, erythrocytes, and platelet and leukocyte components. Physiologic alteration in the levels of nearly all of the coagulation factors occurs during pregnancy. All coagulation factors are increased during pregnancy with the exception of factors XI and XIII, which are frequently decreased. In addition, free protein S levels are physiologically decreased and acquired resistance to activated protein C commonly occurs during pregnancy. Protective mechanisms include the inactivation of activated coagulation factors by circulation inhibitors, clearance of these activated coagulation factors by the liver, dissolution of fibrin by circulating inhibitors, and dissolution of fibrin by circulating fibrinolytic enzymes. The activated blood coagulation factors are serine proteases that are inhibited by the naturally occurring protease inhibitors: antithrombin III, protein C, heparin cofactor II, C-1 inactivator, $\alpha$-2-macroglobulin, and $\alpha$-1-antitirypsin. Hemostatic activation is furthermore indicated by increases in fragment F1 + 2 and D-dimer.[4]

Risk for thromboembolism is furthermore magnified by compression of the inferior vena cava and iliac vein by the pregnant uterus producing venous obstruction, and an increase in venous capacitance promoting stasis. By 25 to 29 weeks gestation, venous flow velocity is reduced by approximately 50% in the legs and does not return to normal nonpregnancy flow velocity rates until around 6 weeks postpartum.[5] During pregnancy, local damage to pelvic veins may occur during vaginal and especially cesarean delivery that provide an environment for an increased risk for thrombosis.

When these physiologic coagulation changes combine with genetic predisposition conditions such as thrombophilias, socio-environmental factors, and other medical factors (obesity, inactivity, and cesarean) the risk for thromboembolism is logically increased.

## INCIDENCE OF VENOUS THROMBOEMBOLISM

According to a metaanalysis, two thirds of deep venous thrombosis events occur in the antepartum period and are equally distributed across trimesters,[6] whereas a preponderance of pulmonary embolism occurs in the postpartum period.[3]

There are many risk factors for venous thromboembolism in pregnancy. More often in current obstetric practice, women are confined to bed rest for prolonged periods

of time during pregnancy. Patients on prolonged bed rest are significantly more likely to develop a venous thromboembolism; a risk further magnified by surgical procedures. Inherited thrombophilias, antiphospholipid antibody syndrome, and earlier history of thrombosis are risk factors for increased risk during pregnancy and postpartum.[2] Additional risk factors during pregnancy include smoking, multiple gestations, age greater than 35 years, obesity, cesarean delivery, and medical complications such as diabetes, heart disease, and sickle cell disease.[7]

## THROMBOEMBOLISM IN INHERITED AND ACQUIRED ANTICOAGULATION DEFICIENCIES

The plasma anticoagulant system of protein S, protein C, antithrombin III (AT-III), and plasminogen-plasmin system inhibit the activity of activated clotting factors and counter the tendency of hypercoagulability seen in normal pregnancy. Thrombophilias are disorders of hemostasis that predispose to thrombotic events. When congenital or acquired deficiencies of these plasma anticoagulants are present, the protection of the normal plasminogen-plasmin interaction is lost and the chances for a thrombotic event during pregnancy increases. The prevalence of inherited thrombophilias depends on the population and/or ethnicity. Approximately 15% of Western populations are affected. Approximately 50% of cases of venous thromboembolism in pregnancy are associated with an inherited or acquired thrombophilias.[8]

Antithrombin III (AT-III), is the major plasma inhibitor of thrombin. Antithrombin III is also capable of inactivating other components of the coagulation cascade, including Factor IXa, Xa, XIa, and XIIa, and plasmin and kallikrein. Antithrombin III neutralizes hemostatic enzymes and protects natural surfaces against thrombus formation. AT-III deficiency shows autosomal-dominant inheritance. The absolute risk of venous thromboembolism for pregnant women with AT-III deficiency is reported to be as high as 40% to 68%.[8] Protein C, in its active form, is responsible for inactivation of factors V and VIII and activation of fibrinolysis. Protein S is a vitamin K-dependent, naturally occurring inhibitor of hemostasis that is synthesized and released from the endothelium and shows autosomal dominant inheritance. It is a cofactor for protein C in the neutralization of activated factor V and in fibrinolysis. The incidence of thromboembolism has been reported to be 2.5% per year for protein C-deficient individuals, and 3.5% per year for those with protein S deficiency.[8] Protein C deficiency is also autosomal dominant, and the heterozygous trait results in plasma protein C levels of 55% to 65% of normal. During pregnancy, an incidence of DVT up to 25% has been reported for heterozygote protein C-deficient individuals.[8] The risk for stillbirth is also increased in women with these protein deficiencies.

Activated protein C resistance results from a point mutation in the factor V gene and is the most frequent etiology for thrombosis. The gene mutation is inherited as an autosomal dominant trait and is particularly prevalent in the white population. Heterozygosity for the factor V gene defect confers a 5 to 10 fold increase risk for thrombosis. Homozygosity for factor V Leiden carries a 50 to 100-fold increased risk for thrombosis.[8]

Acquired thrombophilias include antiphospholipid antibodies and lupus anticoagulant. These conditions are typically diagnosed in women with recurrent pregnancy loss rather than thromboembolism. However, both disorders should be considered as risk factors for thromboembolism during pregnancy. For antiphospholipid antibody syndrome, the absolute risk for thrombosis has been reported to be as high as 30%.[8]

As thromboembolism is still considered a rare event during pregnancy,

screening all pregnant women for the presence of an inherited thrombophilias is not considered cost-effective. The levels of many of these factors, such as Protein S are physiologically lowered by pregnancy and may not truly reflect an actual deficiency. The exception is AT-III and Factor V Leiden. However, a thrombophilia work-up should be considered after pregnancy in those women who have had a thromboembolic event to define management in subsequent pregnancies.

## CLINICAL PRESENTATION AND DIAGNOSIS OF THROMBOEMBOLIC DISEASE

During pregnancy, venous thromboembolism may present with symptoms of DVT, or with the symptom complex consistent with the occurrence of pulmonary embolism. The most common symptoms of DVT are pain, tenderness, and swelling of the lower extremity. Most DVT cases present in the left leg. This is likely owing to the compressive effects on the left iliac vein as it is crossed by the right iliac artery. Isolated deep vein thrombosis in the iliac vein is thought to be higher in pregnancy compared with the nonpregnant women. Clinical signs such as warmth, color, asymmetric change in the width of the leg or thigh, edema, and a palpable cord may be present. The signs and symptoms result from obstructed venous return and/or in combination with vascular inflammation. Clinical diagnosis becomes more suspicious when calf pain is elicited on passive dorsiflexion of the foot (Homan sign).

Thigh swelling is especially relevant because the risk of pulmonary embolism is associated with femoral or iliac thrombosis. Most clinically significant pulmonary emboli occur from thrombi deep in the thigh. Symptoms of pulmonary embolus include dyspnea, pleuritic chest pain with or without splinting, apprehension, and cough. Tachypnea occurs in more than 90% of patients. Other clinical signs include tachycardia, atelectatic rales, hemoptysis, fever, diaphoresis, friction rub, cyanosis, and the development of an accentuated second heart sound, gallop, or murmur. In cases of massive pulmonary embolism defined as obstruction of more than 50% of the pulmonary circulation, hypotension, syncope, or cardiovascular collapse may be the presenting symptoms.

## DIAGNOSIS OF THROMBOEMBOLISM

Clinical suspicion for DVT requires a sensitive test to confirm the diagnosis as many of the classical signs and symptoms of thrombosis including leg swelling, tachycardia, tachypnea, and dyspnea are associated with normal pregnancy changes with advancing gestation. Pulmonary embolism is a significant complication of pregnancy that can lead to sudden death. As such, all pregnant women with signs and symptoms suggestive of thromboembolism, especially symptoms of pulmonary embolism should be tested by the best available modalities and therapy instituted expeditiously to prevent mortality.

## DIAGNOSTIC EVALUATION TEST FOR THROMBOEMBOLISM

Noninvasive test can provide diagnostic information for thromboembolism at less cost and less discomfort with no exposure to ionizing radiation. Doppler flow studies with compression sonography are the primary noninvasive tests used in diagnosis of DVT. Compression ultrasonography is a minimal risk procedure and has a sensitivity of 97% and a specificity of 94% for the diagnosis of symptomatic, proximal deep-vein thrombosis in the general population.[9] Doppler combined with real time ultrasound and color flow has become the diagnostic studies of choice in cases of suspected proximal vein thrombosis. Ultrasound imaging provides additional information about venous compressibility. Acute DVT is diagnosed when a distended vein is identified and cannot be completely

compressed. This process of color flow with compression sonography, is widely accepted as an accurate diagnostic tool for diagnosis of a proximal DVT.

The diagnosis of isolated left calf and deep vein thrombosis of the iliac vein in symptomatic pregnant women is compromised by compression ultrasound because ultrasound does not reliably detect thrombosis in the iliac veins.[9] When using ultrasonography, the use of high pressure to compress the femoral vein in the groin or the absence of flow on Doppler studies is suggestive of iliac vein thrombosis.

Magnetic resonance imaging (MRI) using a gradient recalled echo technique has been used in the diagnosis of iliac-vein thrombosis in pregnant woman. The sensitivity for thrombi above the knee is nearly 100%, but somewhat lower in the calf. MRI can be used to evaluate the patient suspected having a pelvic thrombus with a negative Doppler/ultrasound examination.

Computerized tomography scanning, unlike ultrasonography and MRI is associated with fetal radiation exposure. Computerized tomography scanning is useful for detecting iliac vein thrombosis when MRI is not available.

D-dimer is a specific degradation product of cross-linked fibrin. Levels of D-dimer are increased in the presence of thrombi. However, levels of D-dimer also increase with the progression of normal pregnancy. Interpretation depends on the test used to carry out the assay and laboratory cut-off values. A low concentration of plasma D-dimer might be used to rule out venous thromboembolism in clinically suspected patients. However, the use of D-dimer in pregnancy should be in combination with other tests.

Like DVT, the diagnosis of pulmonary embolism (PE) is difficult to confirm on clinical grounds alone. Diagnostic tests must be used to dictate management in cases of suspected PE (Fig. 1). Patients with suspected PE and normal findings on compression ultrasound must undergo additional diagnostic tests. This begins with a chest radiograph to rule out other diagnoses for the patient's symptoms. Guidelines for evaluation of PE in pregnancy attempt to balance diagnostic efficacy, decreasing maternal morbidity and mortality, and minimization of fetal exposure to ionizing radiation.

The most commonly used noninvasive study is the ventilation-perfusion scan (V/Q scan). Technetium (99 mTc)-labeled albumin microspheres injected intravenously is trapped in the pulmonary capillary bed, thus, accurately depicting the distribution of pulmonary blood flow. The vascular perfusion scan is coupled to a ventilation scan to enhance overall specificity. The Prospective Investigation of Pulmonary Embolism Diagnosis was a large, prospective, multicenter trial that examined the diagnostic use of the ventilation-perfusion scan.[10] Eighty-eight percent of patients with a high-probability scan had angiographic evidence of PE. The study also showed that the combination of clinical assessment and the ventilation-perfusion scan improved diagnostic accuracy.[10] The diagnosis of PE was accurate in patients with a high-probability scan and high-clinical probability. A normal or near normal scan or a low-probability scan in a patient with low-clinical suspicion excluded the diagnosis of PE. Indeterminate scans or low probability scans with high clinical suspicion were not helpful in the diagnosis of PE. These patients required additional test to establish the correct diagnosis. Ventilation-perfusion lung scanning delivers a higher fetal dose of radiation (640 uGy to 800 uGy) than does computer tomographic pulmonary angiography (CT PA) that delivers 3 uGy to 131 uGy.[11] By using 37 to 74 MBq of macroaggregates of human serum albumin labeled with technetium 99 m, the fetal dose from lung scanning is approximately 100 to 370 uGy, which is considered a relatively low radiation exposure to the fetus. Perfusion scanning alone reduces radiation exposure.[11]

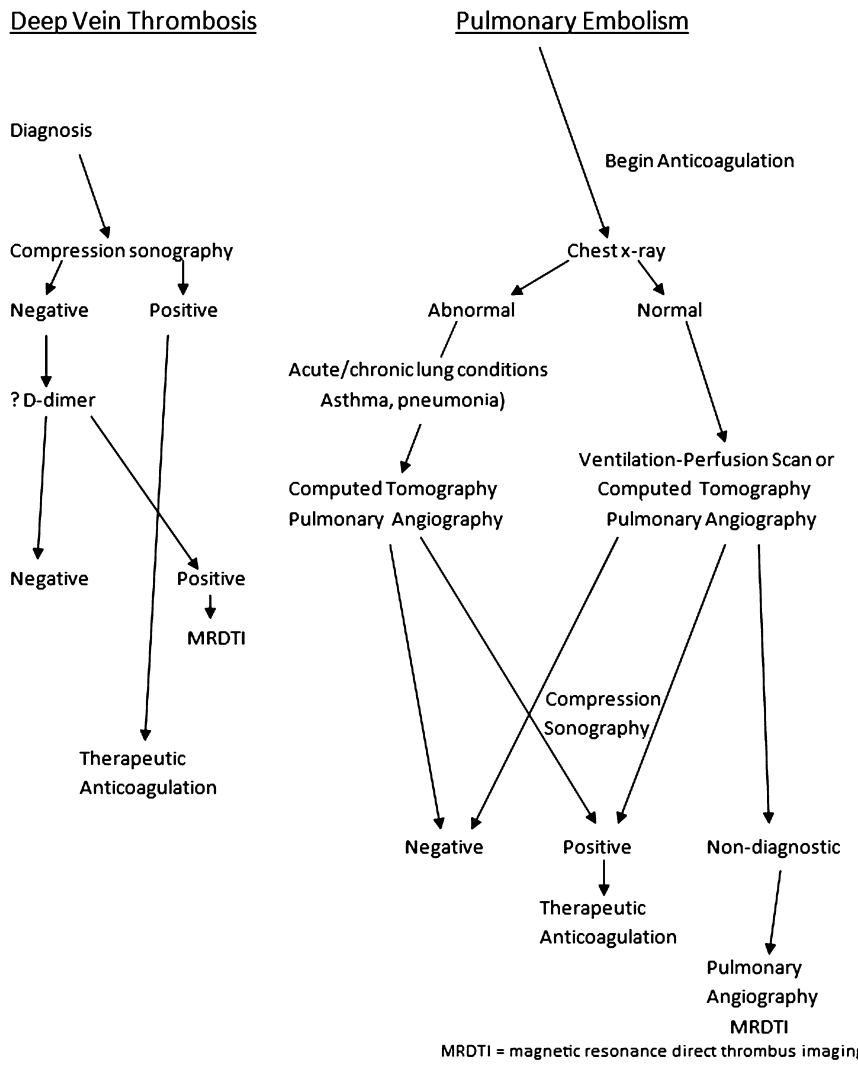


***FIGURE 1.*** Clinical management algorithm for suspected thrombosis during pregnancy and the puerperium. MRDTI indicates magnetic resonance direct thrombus imaging.

Both computed tomography (CT) and MRI have been evaluated as diagnostic tools for suspected PE. Limitations, include the appearance of intersegmental lymph nodes as segmental emboli, inadequate opacification of upper lobe arteries, and difficulty imaging the right middle lobe and lingular segments.[12]

Although diagnostic sensitivity with helical CT is not in question, the concerns about fetal radiation exposure and implication of breast radiation on long-term risk of breast cancer remain. Helical CT is indeed an accurate tool for diagnosis of PE in main, lobar, and segmental pulmonary arteries, but is less accurate for imaging peripheral emboli in subsegmental vessels.[12] For diagnosis of PE, the administration of intravenous contrast is necessary. For helical CT, estimated mean fetal doses of radiation vary with gestational ages, 3.3 to 20.2 uGy in the first trimester,

7.9 to 76.7 uGy in the second trimester, and 51.3 to 130.8 uGy in the third trimester.[13] These doses are less than mean fetal doses reported with scintigraphy.

Advances in MRI technology make the diagnosis of pulmonary embolus possible using this imaging method. MRI has been compared with conventional pulmonary angiography with the sensitivity of MRI ranging from 90% to 100% and the specificity ranging from 62% to 77%.[12]

Standard pulmonary angiography had traditionally been reserved for patients with nondiagnostic ventilation-perfusion scans. In angiography, the diagnosis is made by the visualization of an intraluminal filling defect or an abrupt cut-off of a pulmonary artery. The limitations and complications of angiography are well known. Limitation includes cost, technical expertise, and difficulties in accessing the tertiary pulmonary arteries and nonfatal major and minor complications.

Ventilation-perfusion scanning carries a slightly higher risk of childhood cancer in offspring than CTPA (1 case in 280,000 versus $< 1$ in 1 million). Ventilation perfusion scanning has a lower long-term risk for breast cancer with a lifetime risk up to 13% greater with CTPA than with ventilation perfusion scanning.[13]

The use of any of the modalities mentioned will vary depending on their availability. Typically those women having a DVT on clinical grounds are initially evaluated by compression sonography. Women suspected of having a pulmonary thrombus are evaluated by ventilation-perfusion scans or scintigraphy. Prior episodes of PE may cause a false-positive scintigraphy.[10] Patients with indeterminate results are evaluated by compression sonography to determine if an asymptomatic DVT is present. If a DVT is not detected, these patients are candidates for CT pulmonary angiography (Fig. 1).

During pregnancy, clinicians are reluctant to order or carry out CT as an imaging test for the diagnosis of PE. It is important that clinicians appreciate that CT is safe and accurate for diagnosing PE in main, lobar, and segmental pulmonary arteries. Pregnancy must not interfere with using the most appropriate diagnostic imaging studies for the suspected PE because of the significant risk of morbidity and mortality for both the mother and the fetus.

## MANAGEMENT OF THROMBOEMBOLISM DURING PREGNANCY

### *Anticoagulation*

Anticoagulation is recommended for the treatment of established DVT or PE occurring during pregnancy and the puerperium, and for prophylaxis against venous thromboembolism in women with a history of earlier thromboembolic episodes. Anticoagulation is also indicated for those women considered to be at risk because of the presence of a thrombophilic state. Heparin, unfractionated or low molecular is the anticoagulant of choice for treatment of thromboembolism during pregnancy, and management requires an individualized, well-planned approach. Heparin consists of alternating chains of glucosamine and uronic acid and requires the presence of a specific pentasaccharide sequence capable of binding with high affinity to antithrombin to achieve its anticoagulant properties. The molecular weight in standard unfractionated commercial heparin preparation ranges from 4000 to 40,000 Daltons. This high molecular weight prevents heparin from crossing the placenta, giving the advantage over warfarin preparation, which crosses the placenta and poses teratogenic fetal risk with exposure in the first trimester. Low molecular weight heparin does not cross the placenta. Heparin is not excreted into breast milk. Heparin exerts its anticoagulant activity by binding to AT-lll. Nonspecific binding contributes to the variability in the dose-response on unfractionated heparin.

Small amounts of heparin can inhibit the initial steps of the clotting cascade. After a thrombus is formed, more heparin is needed to neutralize thrombin and prevent extension of the clot. The half-life of heparin varies with the dose and the extent of active thrombosis. Half-life range from less than 1 hour to more than 2½ hours, with a higher dose resulting in a higher peak and a longer half-life. The half-life is inversely proportional to renal and hepatic function. Lower molecular weight heparin (LMWH) preparation (4000 to 5000 Daltons) have a more uniform activity in that they exhibit less binding to plasma proteins and to the endothelial cells.

Low molecular weight heparin has a more predictable dose-response, more dose-independent mechanisms of clearance, and longer plasma half-life than unfractionated heparin. An additional advantage of low molecular weight preparations is that the drugs can be administered in a once or twice-daily subcutaneous injection in fixed or weight-adjusted doses, without laboratory monitoring or dose adjustment.

The primary risk of unfractionated heparin is bleeding. Unfractionated heparin can be rapidly reversed with protamine sulfate in cases of overdose or at the time of emergency surgery, such as cesarean delivery whereas LMWH are not easily reversed. The primary hemostatic defense in heparinized patients is platelet aggregation. Drugs, such as aspirin, that interfere with platelet number or function may increase risk for bleeding.

Other adverse effects of heparin include thrombocytopenia (HIT), hypersensitivity, and osteoporosis. The incidence of thrombocytopenia is variable. An alternative method of anticoagulation should be sought for those patients exhibiting heparin-induced thrombocytopenia. Bone demineralization in pregnancy has been associated with high and prolonged doses of unfractionated heparin. Unfractionated heparin carries a 2% to 36% risk of reduced bone density and a low risk for vertebral fracture.[14]

Low molecular weight heparin is associated with lower risk of bleeding complications and heparin-induced thrombocytopenia and heparin-induced osteoporotic fractures.[14] Current guidelines now recommend LMWH over standard unfractionated heparin for anticoagulation during pregnancy and into the puerperium.[15]

## THERAPY FOR ACUTE DEEP VEIN THROMBOSIS-THROMBOPHLEBITIS

Anticoagulation during pregnancy must be tailored to meet the needs of the women during the antepartum, intrapartum, and postpartum periods. This tailored approach may involve initiation of full-dose heparin anticoagulation before delivery, withdrawal of heparin during delivery, and restarting heparin in the postpartum period. If unfractionated heparin is used for initial anticoagulation, the dose should be administered to prolong the partial thromboplastin time (PTT) 1.5 to 2 times over the normal baseline, or a heparin level of 0.2 to 0.4 U/mL.

For acute DVT, full anticoagulation with LMWH or unfractionated heparin is usually recommended for symptomatic pregnant women as most iliofemoral thromboses originate from calf-vein thrombosis. Unlike nonpregnant patients with DVT with no symptoms of pulmonary embolism who can be treated as an outpatient; anticoagulation for pregnant women with DVT is best initiated as an inpatient. Adequate anticoagulation can be achieved with either subcutaneous or continuous intravenous infusion.

Unfractionated heparin is usually initiated with a bolus intravenous doses of 70 to 100 U/kg, about 5000 to 10,000 U, followed by continuous intravenous infusion beginning at 1000 U/h or 15 to 20 U/kg/h. In the initial management phase, the PTT should be monitored every 4 to 6

hours and adjustment made until an adequate and stable prolongation of the PTT is achieved. After stabilization of the heparin dose, laboratory monitoring of the PTT may be obtained at 24 to 48-hour intervals. Dosages resulting in prolongation of the PTT higher than 2.5 to 3.0 times normal are associated with a higher risk of maternal bleeding. As the active thrombosis resolves there is a reduced need for heparin and the infusion should be adjusted.

The duration of intravenous anticoagulation depends on the severity of the thromboembolic condition. After continuous intravenous infusion treatment, anticoagulation with unfractionated or LMWH is continued with therapeutic subcutaneous injection for the duration of pregnancy and for at least 6 weeks postpartum.

Although the primary mode for initiation of anticoagulation with unfractionated heparin for DVT in pregnancy has been by continuous intravenous infusion route, heparinization also may be initiated through the subcutaneous route. After loading the patient with 150 U/kg intravenously, the patient can be given 20,000 units of heparin subcutaneously every 12 hours. The PTT should be checked at midinterval. Dosing intervals of every 8 hours is popular. There is no difference in efficacy between 8 and 12 hour dosing regimens. Subcutaneous therapeutic heparinization has a lower rate of thrombus extension and bleeding complications than continuous intravenous infusion. Peak levels occur approximately 2 to 4 hours after subcutaneous injection and the lowest level before the subsequent injection. The PTT can be checked weekly after a stable subcutaneous dose is reached and adjustments made accordingly to maintain the PTT 1.5 to 2.0 times the control.

The current management approach for acute DVT during pregnancy is with twice daily weight-based dosing of LMWH. Some clinicians give single dosing to simplify therapy for women with acute DVT and no symptoms of pulmonary embolism. A dosage of 1 mg/kg every 12 hours given subcutaneous is appropriate for acute DVT treatment in pregnancy. This therapeutic dose should be continued for at least 5 days of the acute symptomatic phase of the DVT and maintained for the duration of pregnancy. Patients may be monitored with antifactor Xa activity levels periodically. However, in most pregnant women except those very overweight or underweight or those with impaired renal function, dose adjustments are not necessary.

Long-term anticoagulation also may be achieved by the continuous subcutaneous route using the subcutaneous infusion pump method, or intravenously through centrally placed Hickman catheter for those requiring long term IV anticoagulation. These delivery routes can sometimes have an advantage for those who are noncompliant or those who want to avoid intermittent injections.

Low molecular weight heparin dosing regimens vary.[15] Although rare, cutaneous allergic reactions can occur, which present as pruritus and urticarial rashes and rarely skin necrosis. These reactions are more common with long-term use of LMWH. If reactions occur, patients may be switched to another LMWH preparation. Cross reactivity occurs in approximately one-third of women switched to another preparation of LMWH. The form of LMWH, fondaparinux, is a synthetic pentasaccharide and direct inhibitor of factor Xa and has been suggested as a safe alternative in women with cross reactivity.[16] The FDA has designated fondaparinux as a pregnancy category B drug.

## ANTICOAGULATION FOR LABOR AND DELIVERY

The pregnant woman receiving a therapeutic anticoagulation regimen should be given strict instructions as to what to expect during the intrapartum period. Anticoagulated patients are at risk for

bleeding complications associated with delivery. As such, management of anticoagulation toward the end of pregnancy needs coordination between the provider and the patient to minimize risk and to plan for the anticipated regional anesthesia that most women will desire for vaginal delivery or cesarean. For women on therapeutic IV heparin as might be the case for acute pulmonary embolism, the doses should be stopped 6 hours before placement of a neuraxial block and a normal activated partial—thromboplastin time should be confirmed before proceeding with the block. If a cesarean must be emergently carried out for the therapeutically anticoagulated patient, the preferred method of anesthesia is general intubation.

According to the current guidelines of the American Society of Regional Anesthesia and Pain Medicine, spinal anesthesia may be carried out 12 hours after the last dose of prophylactic and 24 hours after therapeutic LMWH dosing.[17] It is reasonable to switch women from subcutaneous LMWH to subcutaneous unfractionated heparin around 36 weeks gestation because of the unpredictability of the onset of labor and/or the potential for emergency cesarean. As the pharmacokinetics of subcutaneous unfractionated and LMWH are similar, this practice of switching from LMWH to unfractionated heparin several weeks before planned delivery or at term probably has limited benefit as an evidenced-based approach to clinical practice and is mostly a matter of convenience.

Ideally, the woman on prophylactic LMWH is switched to 5000 to 7500 U of unfractionated subcutaneous heparin at least 1 to 2 weeks before anticipated labor or admission for induction or cesarean delivery. The patient is instructed to avoid her next scheduled injection of heparin when regular uterine contractions begin. If she happens to present to labor before switching from LMWH to unfractionated heparin she should be advised to hold the next scheduled dose of heparin. On admission to labor, a clotting profile should be obtained. If delivery is likely within 12 hours of admission, several options are available, depending on the seriousness of the thrombotic condition. For the more high-risk woman, such as may be the case with recent pulmonary embolus or labor during the active deep vein thrombosis stage, continuation of therapeutic heparinization may be the best option if vaginal delivery can be anticipated. However, if cesarean delivery becomes necessary, more blood loss should be anticipated. If time allows, unfractionated heparin can be adjusted downward or reversed with protamine sulfate until it is safe to resume the therapeutic dose. Protamine sulfate would be indicated if the PTT is higher than 60 seconds with an emergency cesarean, or in the second stage of labor to minimize bleeding from perineal injury. A dose of 1 milligram of protamine sulfate for every 100 units of heparin will quickly shorten the PTT. One must be reminded that excessive protamine sulfate may act as an antithrombin. Therefore, larger doses than those recommended should be avoided. Except for perineal injury hematoma, women having vaginal delivery experience no more blood loss whether receiving therapeutic anticoagulation or prophylaxis. Uterine hemostasis is not affected by heparinization. Fear of bleeding, with consequent neurologic damage, has lead to a cautious approach to regional anesthesia in women receiving anticoagulation during labor and delivery.

Another alternative in the intrapartum period would be to discontinue the therapeutic heparin regimen in favor of prophylaxis with 5000 units every 12 hours, or to withhold intravenous or subcutaneous injections when within 6 to 8 hours of delivery. Depending on the dose, 6 to 8 hours should allow enough time for the PTT to significantly shorten and decrease the risk for excessive bleeding.

During the postpartum period, the clinician must balance the additive risk for thromboembolism against the need for continued anticoagulation. In most instances, anticoagulation may be resumed within 12 hours of vaginal delivery and 24 hours after cesarean delivery.[2] Therapy may be reinitiated through the subcutaneous route with LMWH in approximately 12 hours and adjusted to a therapeutic range if required based on indication and if there is no evidence of persistent bleeding. If the patient has had a neuraxial anesthetic, therapeutic dosing should wait until 24 hours postoperative or postpartum.[17] For DVT occurring antepartum, the regimen is usually continued for 6 weeks postpartum.

In the postpartum period, anticoagulation with warfarin is a responsible alternative to heparinization. The patient may be bridged with warfarin within 72 hours. Heparin and warfarin should be given concurrently until a therapeutic warfarin effect is achieved. A therapeutic warfarin range is considered to be at a target international normalized ratio (INR) of 2.0 to 3.0 for oral anticoagulation in a patient with a first-time DVT. Warfarin is continued at a therapeutic dose for 6 to 12 weeks, depending on the prior thromboembolic event. Although warfarin therapy in lactating women remains controversial, it is not contraindicated. Warfarin is associated with a higher risk for bleeding complications than with heparin, and requires close monitoring of the INR.

Postthrombotic syndrome occurs in up to 60% of patients after a deep-vein thrombosis.[18] Wearing compression stocking on the affected leg after the acute event reduces the risk of this complication.[18]

## THERAPY FOR PULMONARY EMBOLUS

Acute treatment for pulmonary embolism during pregnancy includes prompt therapeutic anticoagulation with intravenous heparin, supplemental oxygen, and coordinated multidisciplinary care in a tertiary care center capable of dealing with the critical care implications of the mother, baby, and cardiopulmonary complications. Two-third of patients who ultimately die from PE do so within 30 minutes of the acute event; before anticoagulation can have an effect on mortality. Therefore, if the clinical picture strongly suggests PE, anticoagulation should be initiated before diagnostic studies to prevent further embolic events whereas awaiting confirmatory diagnosis.

Once the diagnosis of acute pulmonary embolism is confirmed in the pregnant patient, in addition to therapeutic anticoagulation, a temporary vena cava filter might also be considered if there is serious concern for continuous embolism. The same principles for therapeutic anticoagulation as for DVT should be followed for acute pulmonary embolism except the severity and risk for mortality dictates judicious anticoagulation and hence, a rational intravenous approach is taken to reach the therapeutic anticoagulation goals.

The primary purpose of anticoagulation in the patient with a PE is to prevent reembolization. Treatment of acute PE requires anticoagulation and cardiovascular support. Heparinization is usually initiated with loading dose of 110 to 120 U/kg intravenously; followed by a continuous infusion to maintain the PTT at 2 times normal. Therapeutic intravenous heparinization should be continued for several days followed by therapeutic subcutaneous therapy for the duration of the pregnancy and for 12 weeks postpartum. If the pulmonary embolus occurs in the postpartum period, warfarin may be initiated after several days of intravenous heparinization. The subcutaneous route is avoided in the initial management of acute PE because of the delayed absorption of 2 to 4 hours, which is a critical and vulnerable period of reembolization.

If the pregnant woman requires delivery during the acute therapeutic treatment phase of this critical illness, full anticoagulation is discontinued and reversed with protamine once in active labor or in preparation for cesarean delivery. Although in labor the patient can remain on low-dose heparin 5000 to 7500 U q 12 hours. If the patient requires an emergency cesarean delivery for severe maternal or fetal compromise then care must be coordinated between the maternal fetal medicine specialist, intensivist, anesthesiologist, and cardiopulmonary specialist. Care coordination and management strategies are dictated by the critical nature of the women's illness and hemodynamic status of the women.

## INFERIOR VENA CAVA INTERRUPTION

Inferior vena cava interruption is indicated when anticoagulation is contraindicated, as may be the case with hemorrhagic complications of cesarean delivery, or is ineffective in preventing recurrent emobilization, placing the pregnant, or postpartum woman at risk for greater morbidity or mortality.

Interruption of the inferior vena cava may be effective in preventing reembolization in such situations because most pulmonary emboli originate from venous thrombi of the lower extremities or pelvis. For the pregnant or postpartum female, the filter should be placed in the suprarenal vena cava rather than the standard infrarenal position as the left ovarian vein empties into the left renal vein. Vena caval interruption using filters also has been recommended in conjunction with low-dose heparin in the acute management of DVT to achieve the objective of prevention of pulmonary embolism and to minimize the long-term sequelae of postphlebitic changes.[19] Currently, most filters that are used for vena caval interruption are temporary and retrievable.

## THROMBOLYTIC THERAPY

Thrombolytics, such as streptokinase, urokinase, and tissue plasminogen activator, have been used in the treatment of pulmonary embolism. Thrombolytic therapy is relatively contraindicated in pregnancy, and their use should be avoided close to the time of delivery and shortly postpartum owing to the risk of hemorrhage. Thrombolytics should be reserved for use in preventing reembolization and death in the pregnant woman who are in need of drastic measures to improve survival.[20] In this situation, the use of thrombolytic therapy that is traditionally considered to be a contraindication in pregnancy may be appropriate and life saving. Withholding such therapy for a woman with massive pulmonary embolism and hemodynamic instability does no service to her or her unborn child considering the risk for mortality.

When thrombolytic therapy is contraindicated and pulmonary embolism is life-threatening, emergency pulmonary embolectomy is a reasonable option. For example, massive emboli may require cardiopulmonary bypass and embolectomy to save the life of the mother.

## MANAGEMENT OF WOMEN WITH A HISTORY OF PRIOR THROMBOEMBOLISM

Woman with a history of DVT or pulmonary embolism during a prior pregnancy or while on oral contraceptives are believed to be at increased risk for recurrent thrombosis during subsequent pregnancies.[2] In fact, the most significant risk factor for recurrent thrombosis during pregnancy is a history of thrombosis.[2] In such instances, the precipitating thromboembolic event is usually estrogen-mediated, which increases the risk for recurrence in comparison to those individuals who experience a thrombotic event from trauma or nonobstetric surgery. The risk of recurrent thromboembolism in women with a prior pregnancy-related

event has been reported to be 4% to 12%.[2] The risk is 3 to 4-fold compared with women not pregnant (RR 3.5; 95% CI 1.6,7.8).[2] Fifteen to 25% of thromboembolic events in pregnancy are recurrent events.[2] In recent studies, the rate of recurrent venous thromboembolism in at risk women who did not receive anticoagulant prophylaxis ranged from 2.4% to 12.2%.[2] For women who did receive anticoagulation prophylaxis, the rate of recurrent VTE is lower.

Although there is no absolute consensus on the need for prophylaxis, nor the most appropriate regimen, most clinicians feel that it is appropriate for women with a prior history of thrombosis during pregnancy to receive anticoagulant prophylaxis with a subsequent pregnancy. The usual treatment regimen for women with a prior DVT includes prophylactic with 5000 U unfractionated subcutaneous heparin or LMWH 40 mg daily or 30 mg twice daily before 28 weeks and 40-mg bid after 28 weeks, throughout pregnancy, discontinuation at delivery, and resumed administration for up to 6 weeks postpartum. The activated PTT is an insensitive method to detect the anticoagulant effects of low-dose heparin. Heparin assays using an anti-Xa method may be more practical for such patients with the goal of maintaining heparin levels between 0.08 and 0.15 unit/mL, 3 hours after injection. A regimen of 5000 units every 12 hours may be insufficient to prevent thromboembolic events after the first trimester. Therefore, the heparin dose should be increased to 7500 units every 12 hours, beginning at approximately 8 to 13 weeks gestation and to 10,000 units every 12 hours in the third trimester (> 28 wk) for more effective prophylaxis.[2] The increase may be especially relevant for the women who had a PE as the prior thrombosis event. Full dose (adjusted dose) or moderate dose anticoagulation is recommended for those women with a need for life-long anticoagulation (AT-III, homozygosity for factor V Leiden mutation, prothrombin gene G20210A mutation, or combined heterozygosity for both mutations) or antiphospholipid antibody syndrome with a history of thrombosis.[2] Women with high-risk thrombophilias should receive antenatal and postpartum thromboprophylaxis even though they do not have a history of a venous thromboembolic event.[15] For women with a history of unprovoked thrombosis, low-dose anticoagulant prophylaxis is recommended. However, an option for women with a history of thrombosis while not pregnant and in the setting of transient risk factors of injury or immobility or when the risk factor is no longer present may be closely observed without thromboprophylaxis.[19] These women may be candidates for thromboprophylaxis in the first 2 to 6 weeks postpartum because of the vulnerability for thromboembolic events to occur during the puerperium.[2]

Thromboprophylaxis should be considered for morbidly obese pregnant women (BMI > 40) and those confined to bed for prolonged periods (premature rupture of membranes, placenta previa, etc). The use of pneumatic compression devices for the prevention of pregnancy-related thrombosis has not been well studied and risks are primarily extrapolated from perioperative data.[21] However, intermittent pneumatic compression devices have been shown to be safe, efficacious, and cost effective in moderate and high-risk patients such as those undergoing gynecologic surgery.[21] In a randomized comparison of mechanical prophylaxis with pneumatic compression foot pump versus chemoprophylaxis for deep-vein thrombosis, DVT was detected in 3 of 100 patients in the foot pump group compared with 6 of 100 patients in the LMWH group ($P < 0.05$).[22]

Pulmonary embolism after cesarean delivery is higher than after vaginal delivery by a factor of 2.5 to 20, and the

incidence of fatal pulmonary embolism by a factor of 10.[23] Therefore, it would stand to reason that for pregnant women at the greatest risk for thromboembolism such as those on prolonged bed rest, BMI $>40$ and requiring cesarean delivery the use of pneumatic compression devices for the prevention of pregnancy related thrombosis has merit.

The duration of thromboprophylaxis after cesarean for this high-risk group has not been studied. As the risk of peripartum deep-vein thrombosis is highest during the first week or so postpartum, it is not unreasonable to continue mechanical means with compression stocking or boots, or chemoprophylaxis with low-dose LMWH for the first couple of weeks after delivery for the high-risk patient.[15]

## Conclusions

Venous thrombosis event during pregnancy fortunately remain rare. However, the risk for morbidity and mortality remains significant. The clinician must maintain a high index of suspicious and use appropriate diagnostic modalities to institute immediate anticoagulation therapy if morbidity and mortality is to be minimized. An appropriate and timely evaluation for acquired or hereditary thrombophilic disorders should be considered the standard of care to decrease the risk of recurrent events by instituting thromboembolic chemoprophylaxis in subsequent pregnancies. Pneumatic compression devices are currently underused in pregnant women at greatest risk for embolism such as those with morbid obesity and undergoing cesarean delivery. The use of these devices should be encouraged when appropriate.

## References

1. WHO, the UN Children's Fund, the UN Population fund. Maternal mortality in 1995: Estimates Developed by WHO, UNICEF, and UNFPA, Document WHO/RHR)1.9, World Health Organization, Geneva (2001).
2. James AH, Grotegut CA, Brancazio LR, et al. Thromboemoblism in pregnancy: recurrence and its prevention. *Semin Perinatol*. 2007;31:167–175.
3. 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;143:697–706.
4. Eichinger S, Weltermann A, Philipp K, et al. Prospective evaluation of hemostatic system activation and thrombin potential in healthy pregnant women with and without factor V Leiden. *Thromb Haemost*. 1999;82:1232–1236.
5. Macklon NS, Greer IA. The deep venous system in the puerperium: an ultrasound study. *Br J Obstet Gynaecol*. 1997;104:198–200.
6. Ray JG, Chan WS. Deep vein thrombosis during pregnancy and the puerperium: a meta-analysis of the period of risk and leg of presentation. *Obstet Gynecol Surv*. 1999;54:265–271.
7. Larsen TB, Sorensen HT, Gislum M, et al. Maternal smoking, obesity and risk of venous thromboembolism during pregnancy and the puerperium: a population-based nested case-control study. *Thromb Res*. 2007;120:505–509.
8. Nelson SM, Greer IA. Thrombophilia and the risk for venous thromboembolism during pregnancy, delivery and puerperium. *Obstet Gynecol Clin North Am*. 2006;33:413–427.
9. Kearon C, Julian JA, Newman TE, et al. Noninvasive diagnosis of deep venous thrombosis: McMaster diagnostic imaging practice guidelines initiative. *Ann Intern Med*. 1998;128:663–677.
10. The PIOPED Investigators: value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). *JAMA*. 1990;273:2753–2759.
11. Groves AM, Yates SJ, Win T, et al. CT pulmonary angiography versus ventilation-perfusion scintigraphy in pregnancy: implications from a UK survey

of doctors' knowledge of radiation exposure. *Radiology*. 2006;240:765–770.
12. Matsumoto AH, Tegtmeyer CJ. Contemporary diagnostic approaches to acute pulmonary emboli. *Radiol Clin North Am*. 1995;33:167–183.
13. Winer-Muram HT, Boone JM, Brown HL, et al. Pulmonary embolism in pregnant patients: fetal radiation dose with helical CT. *Radiology*. 2002;224:487–492.
14. Greer IA, Nelson-Piercy C. Low molecular weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. *Blood*. 2005;106: 401–407.
15. Bates SM, Greer IA, Pabinger I, et al. Venous thromboembolism, thrombophilia antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guideline (8th edition). *Chest*. 2008;133(suppl): 844S–886S.
16. Gerhardt A, Zotz RB, Stockschlaeder M, et al. Fondaparinux is an effective alternative anticoagulant in pregnant women with high risk of venous thromboembolism and intolerance to low molecular weight heparins and heparinoids. *Thromb Haemost*. 2007;97:496–497.
17. Horlocker TT, Wedel DJ, Benzon H, et al. Regional anesthesia in the anticoagulated patient: defining the risks (the second ASRA Consensus Conference on Neuraxial Anesthesia and anticoagulation). *Reg Anesth Pain Med*. 2003; 28:172–197.
18. McColl MD, Ellison J, Greer IA, et al. Prevalence of the posthrombotic syndrome in young women with previous venous thromboembolism. *Br J Haematol*. 2000;108:272–274.
19. Baglin TP, Brush J, Streff BM. Guidelines on the use of vena cava filters. *Br J Haematol*. 2006;134:590–595.
20. Leonhardt G, Gaul C, Nietsch HH, et al. Thrombolytic therapy in pregnancy. *J Thromb Thrombolysis*. 2006;21:271–276.
21. ACOG Practice Bulletin #84, Clinical Management Guidelines for Obstetrican-Gynecologists. Prevention of deep vein thrombosis and pulmonary embolism. Obstet Gynecol, August 2007;110(2), Part 1;429-440.
22. Pitto RP, Hamer H, Heiss-Dunlop W, et al. Mechanical prophylaxis of deep vein thrombosis after total hip replacement. A Randomised Clinical Trial. *J Bone Joint Surg (Br)*. 2004;86-B:639–642.
23. Bonnar J. Can more be done in obstetric and gynecologic practice to reduce morbidity and mortality associated with venous thromboembolism? *Am J Obstet Gynecol*. 1999;180:784–791.