Risk Factors for and Clinical Management of Venous Thromboembolism During Pregnancy

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Abstract: Venous thromboembolism (VTE), which comprises deep vein thrombosis and pulmonary embolism, is one of the leading causes of non-obstetric maternal death in the United States. Physiologic and anatomic changes associated with pregnancy set the stage for a hypercoagulable state. In addition, other risk factors—including those associated with certain fetal characteristics such as low birth weight or stillbirth—have been correlated with an increased risk for VTE. Women with a personal or strong family history of VTE, as well as documented thrombophilia, represent a unique group in whom antepartum and/or postpartum prophylaxis can be considered. The choice of anticoagulant therapy for either treatment or prophylaxis in most cases is heparin, most commonly low-molecular-weight heparin. This is owing to the fact that vitamin K antagonists and the direct oral anticoagulants are contraindicated in pregnancy because of potential teratogenicity. With careful management and vigilant monitoring, appropriate anticoagulation can be used safely and effectively to improve patient outcomes.

Introduction

Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is among the leading causes of non-obstetric maternal death in the United States and other developed nations.[1,2] VTE is responsible for 9.2% of maternal deaths in the United States, with an observed increase in VTE incidence during hospitalization for vaginal delivery from 15.6 per 100,000 deliveries in 2006 to 29.8 per 100,000 deliveries in 2012.[3,4] The VTE risk increases by 4- to 6-fold during pregnancy, and is highest in the immediate postpartum period.[5,6]

The increased risk in VTE is caused by several factors that stem from the physiologic and anatomic changes that take place during pregnancy. Such factors include hypercoagulability, progesterone-induced venous stasis, compression of the inferior vena cava and pelvic veins owing to an enlarged uterus, and decreased mobility. Patients with other intrinsic risk factors, such as prior history of VTE

(either provoked or unprovoked) and/or inherited or acquired thrombophilia, may require either antepartum and/or postpartum thromboprophylaxis.[6]

The main anticoagulants used in pregnancy are unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH), although LMWH is the preferred choice. Owing to their teratogenicity, particularly during the first trimester, vitamin K antagonists (VKAs) are avoided except in women with mechanical heart valves, in whom they are usually prescribed in the second trimester of pregnancy. The direct oral anticoagulants (DOACs) are not recommended in pregnancy owing to potential crossing of the placenta. Heparins and VKAs are safe during lactation, but DOACs are not.[7]

Table 1. Physiologic Changes in Coagulation Factors During Pregnancy

- Increased fibrinogen
- Increased factor VII
- Increased factor VIII and VWF
- Increased factor X
- Increased PAI-1 and PAI-2
- Elevated D-dimer
- Decreased free protein S
- Decreased activated protein C resistance

PAI, plasminogen activator inhibitor; VWF, von Willebrand factor.
Sources: Hellgren M et al. *Semin Thromb Hemost*. 2003;29(2):125-130; Brenner B et al. *Thromb Res*. 2004;114(5-6):409-414.[8,9]

Risk Factors

Physiologic changes occur in pregnant women that confer an increased risk of VTE. Hypercoagulability results from increased levels of coagulation factors I (fibrinogen), VII, and VIII; von Willebrand factor; and factor X. Pregnant women also experience decreased free protein S (a natural anticoagulant), decreased acquired resistance to activated protein C, and decreased fibrinolysis owing to increased levels of plasminogen activator inhibitors 1 and 2 and increased D-dimer levels (Table 1).[8,9]

Patient-related risk factors may increase the individual risk of developing a VTE during pregnancy or the postpartum period. These risk factors include a history of estrogen-related or unprovoked VTE, the presence of severe inherited thrombophilia, and the presence of antiphospholipid antibodies.[10] Other risk factors that enhance the risk of VTE during pregnancy include obesity, older maternal age (>35 years), multiparity, smoking, sickle cell disease, and systemic lupus erythematosus. VTE more commonly presents as DVT in the antenatal period, and as PE in the postpartum period.[11,12]

One prospective cohort study of approximately 1.3 million pregnancies in Denmark revealed other pregnancy-specific conditions that confer an increased risk of VTE. They found that hospitalization for hyperemesis, multiple vs singleton pregnancy, and delivery via cesarean section were associated with a 2.5-, 2.8-, and 1.4-fold increased risk of VTE, respectively.[13] Moreover, maternal age older than 35 years was the most important risk factor for VTE.

A particular group of women with increased risk are those with a history of prior VTE. In an observational cohort study involving 270 pregnant women (369 pregnancies) with at least 1 previous episode of VTE, recurrent VTE occurred in 28 pregnancies (7.6%); of those, 12 recurrent VTEs (3.3%) occurred in 10 women during early pregnancy prior to starting LMWH, and 16 recurrent VTEs (4.3%) developed in 15 women despite LMWH prophylaxis. The risk of antepartum recurrent VTE is considerable in women with a history of 2 or more previous VTEs, hormone-related VTE, the presence of antiphospholipid antibodies, or the need for long-term anticoagulation. Antepartum prophylaxis with prophylactic doses of LMWH or even with intermediate doses of LMWH might not be sufficient in this high-risk population.[14] Another study demonstrated that among women with a prior history of VTE, 6.2% developed a recurrent thrombosis during pregnancy when not on prophylaxis. Moreover, women who had their first VTE in the setting of oral contraceptives had a higher rate of recurrent thrombosis during pregnancy compared with those who had other risk factors for their initial VTE.[10]

Approximately 50% of pregnancy-related VTEs are associated with inherited thrombophilia. A systematic review of 79 studies, in which 9 studies with 2526 patients assessed the risk of VTE associated with inherited thrombophilia in pregnancy, revealed that individuals with thrombophilia had a 0.74 to 34.40 odds ratio (OR) of developing VTE.[16] Although women with thrombophilia have an increased relative risk of developing VTE in pregnancy, the absolute risk of VTE remains low (Table 2).[15-17]

Not only do maternal factors enhance the risk of VTE, so do factors related to the pregnancy or the fetus itself. For instance, one case-control study identified a 3-fold increased risk of postpartum VTE in low-birth-weight deliveries.[18] Other large cohort studies revealed that stillbirth is an independent risk factor for VTE.[19] Preeclampsia increases the risk of VTE by approximately 5-fold.[20] Likewise, women with pregnancies achieved via assisted reproductive techniques have a slightly higher risk of thrombosis compared with women who have natural conception. In these women, the development of ovarian

Table 2. Risk of VTE in Pregnant Women With Various Thrombophilias

Thrombophilia	Asymptomatic Carriers	Positive Family History of VTE	Personal History of VTE
	Estimated absolute risk of VTE events per 1000 patients[a]		
Factor V Leiden (heterozygous)	8	15	100
Factor II G20210A (heterozygous)	6	15	>100
Factor V Leiden (homozygous)	34	70	170
Factor II G20210A (homozygous)	26	70	>170
Antithrombin deficiency	4	20	400
Protein C deficiency	4	20	40-170
Protein S deficiency	3	20	0-220

[a] Assuming a baseline risk of 1 VTE event per 1000 pregnant patients without a known thrombophilia.

VTE, venous thromboembolism.

Sources: Robertson L et al. *Br J Haematol*. 2006;132(2):171-196; Bates SM et al. *Chest*. 2012;141(2)(suppl):e691S-e736S; American College of Obstetricians and Gynecologists Women's Health Care Physicians. *Obstet Gynecol*. 2018;132(1):e18-e34.[15-17]

stimulation syndrome is an independent risk factor for thrombosis.[21]

Diagnosis

In pregnancy, a clinical diagnosis of DVT is less reliable given common findings that may confound standard history-taking and the physical examination. In most pregnant patients with clinically suspected DVT, the diagnosis is not confirmed. Other causes of leg pain and swelling are not uncommon during pregnancy and include cellulitis, ruptured Baker's cyst, and muscle pain. A cross-sectional study described the derivation of the LEFt clinical decision rule, which relies on 3 variables in pregnant women with suspected DVT: left leg presentation (L), calf circumference difference of at least 2 cm (E for edema), and first trimester presentation (Ft). If none of these variables are present, the negative predictive value is 100%.[22] A validation study suggested that a negative LEFt rule accurately identifies pregnant women in whom the risk for confirmed DVT appears to be very low. The rule should not be used as an individual test for excluding DVT during pregnancy, but could be applied in a diagnostic approach in association with D-dimer measurement and compression ultrasonography (CUS); however, it has not been prospectively validated for safety and efficacy.[23] In a study of 149 consecutive pregnant women with suspected DVT, a whole-blood agglutination D-dimer test had a sensitivity of 100% and a specificity of 60%.[24] A 2006 systematic review found only 4 diagnostic studies of VTE in pregnancy in the literature. One of these studies showed that a combination of a negative CUS and normal D-dimer level can accurately exclude DVT.[25] Serial CUS is necessary for pregnant women with a high clinical suspicion of DVT but a negative initial investigation. In a study of 221 pregnant women in whom DVT was clinically suspected, 16 women (7.2%) were diagnosed with DVT by initial CUS, and none were diagnosed with DVT on serial testing. During follow-up (≥3 months), 6 of the 205 women with normal serial CUS results presented with symptoms of DVT, PE, or both, and one of them was diagnosed with DVT and PE. The sensitivity of serial CUS with Doppler imaging was 94.1% (95% CI, 69.2%-99.7%), and the negative predictive value was 99.5% (95% CI, 96.9%-100%).[26] All ultrasounds undertaken for investigation of pregnancy-associated DVT should include imaging of the iliac veins if there is a high index of suspicion and the CUS is negative for femoral DVT. Serial CUS with Doppler imaging of the iliac vein performed over a 7-day period can exclude DVT in symptomatic pregnant women.[26] Repeat CUS may be done 2 to 4 days and 6 to 8 days after the initial scan. Iliofemoral vein thrombosis accounts for approximately 90% of proximal thrombosis in pregnancy, occurring most often in the left lower extremity.[26] The incidence of isolated iliac vein thrombosis in pregnancy is low, but when it does occur, a delay in diagnosis can lead to significant morbidity. Patients with iliac vein thrombosis may present with unexplained inguinal, pelvic, or abdominal pain, which may be accompanied by back pain, and they usually experience swelling of the entire leg. In women with suspected isolated iliac vein thrombosis in whom CUS is negative or nondiagnostic, magnetic resonance direct thrombus imaging (MRDTI) should be performed.[27] MRDTI does not require gadolinium contrast, and its accuracy appears to be similar to that of venography for iliac vein thrombi

in the nonpregnant population.[27] Exposure to gadolinium during pregnancy is associated with an increased risk for rheumatologic, inflammatory, or infiltrative skin conditions and stillbirth or neonatal death.[28] Ovarian vein thrombosis is a rare but serious diagnosis. It occurs mostly in the postpartum period, mainly after cesarean delivery, and usually affects the right ovarian vein. The diagnosis is confirmed by ultrasound, computed tomography (CT), or magnetic resonance imaging.[29]

PE is more challenging to diagnose than DVT during pregnancy. Approximately 1 in 1000 to 3000 pregnancies are complicated by PE.[19] Studies have reported a relatively low rate of diagnosed PE in pregnant women with clinical signs suggestive of this diagnosis, with a prevalence between 1% and 7%.[30] The clinical presentation of PE and associated laboratory testing results may be subtler in pregnant than in nonpregnant patients. The 2011 guidelines from the American Thoracic Society (ATS) and the Society of Thoracic Radiology (STR) recommend against using D-dimer testing to diagnose PE in pregnancy.[31] However, a recent prospective study involving 498 pregnant women with a clinically suspected diagnosis of PE employed the YEARS algorithm and the D-dimer level to diagnose PE. The study assessed 3 criteria from the YEARS algorithm—clinical signs of DVT, hemoptysis, and PE as the most likely diagnosis—and also measured the D-dimer level. PE was excluded if the patient did not have any of the 3 criteria and a D-dimer level less than 1000 ng/mL, or 1 criterion and a D-dimer level less than 500 ng/mL. If a woman had symptoms of DVT, a CUS was performed, and if positive, anticoagulation was initiated. A computed tomography pulmonary angiogram (CTPA) was performed if the YEARS criteria were negative but the D-dimer level was greater than 1000 ng/mL, or if 1 to 3 YEARS criteria were present and the D-dimer level was greater than 500 ng/mL. The primary outcome was the incidence of VTE at 3 months. The secondary outcome was to determine the proportion of patients in whom CTPA could be successfully avoided to exclude PE. PE was diagnosed in 20 women (4%) at baseline and DVT was diagnosed in 1 woman during follow-up. CTPA was avoided in 39% of pregnant women overall, with the highest efficiency in the first trimester.[32] In a recent systematic review and meta-analysis of CTPA and ventilation/perfusion (V/Q) scanning for diagnosing PE during pregnancy, the documented radiation measurements were lower than the established threshold of 100 mGy for both imaging techniques.[30] It has been previously accepted that CTPA results in relatively higher breast radiation but lower fetal radiation exposure compared with V/Q scanning. A recent study showed that the short-term risk of breast cancer is similar after V/Q scanning and CTPA, although the long-term risk of developing breast cancer after CTPA is unknown.[33] If CTPA is recommended to diagnose PE, the patient should be informed that radiation to the breast might increase her baseline risk for breast cancer. The ATS guidelines state that "given the lack of evidence documenting clear superiority of any one diagnostic test, the values and preferences of a patient and her physician likely will and should determine the final choice and sequence of tests performed."[31] The decision should be based on the local availability of scans and the use of optimal protocols designed for the pregnant woman.

Treatment

Anticoagulants

For pregnant patients, treatment of VTE needs careful consideration. Both UFH and LMWH are safe anticoagulants during pregnancy because neither crosses the placenta, and they have been used in pregnancy for many years. In a review of 1325 pregnancies, 186 reports of fetal and infant outcomes following anticoagulant therapy were made. Outcomes in UFH-treated patients were similar to those in the normal population after excluding pregnancies with comorbid conditions that are independently associated with adverse outcomes.[34] A systematic review of LMWH for prophylaxis and treatment of VTE during pregnancy included 64 studies with 277 pregnancies. No maternal deaths occurred, live births resulted from 94.7% of the pregnancies, VTE or arterial thrombosis occurred in 0.86% of pregnancies, and significant bleeding occurred in 1.98% of pregnancies.[35] The standard UFH regimen is an initial bolus of 5000 U intravenously and 10,000 U or more subcutaneously every 12 hours to target an activated partial thromboplastin time (aPTT; 1.5-2.5 × control) measured 6 hours after injection. It has been suggested that the anti-Xa assay with a mid-dosing interval target of 0.3 to 0.7 U/mL is a more reliable measure of therapeutic UFH activity than the aPTT, because aPTT prolongation may be suppressed owing to a pregnancy-related increase in factor VIII activity.[36] LMWH is dosed based on weight; regimens include enoxaparin at 1 mg/kg subcutaneously twice daily or 1.5 mg/kg once daily, or dalteparin at 100 U/kg twice daily or 200 U/kg once daily. Monitoring of the anti-Xa level for assessing the therapeutic range of LMWH during pregnancy remains controversial. If LMWH is monitored, however, a therapeutic peak anti-Xa level (measured 4 hours after the dose) is between 0.6 and 1.0 U/mL and 1.0 to 2.0 U/mL for twice-daily and once-daily regimens, respectively.[37] LMWH has greater reliability; it is easy to use and has fewer side effects than UFH, including lower risk of heparin-induced thrombocytopenia, osteoporosis, and bleeding complications. 2012 guidelines from the American College of Chest Physicians (ACCP) and 2018 guidelines from the American

Society of Hematology (ASH) recommend LMWH over UFH as the first-line treatment for VTE in pregnancy.[15,38]

In certain clinical situations, such as patients with renal dysfunction who have creatinine clearance of less than 30 mL/min, UFH may be indicated. In a study of 103 pregnancies in 93 women given anticoagulation during pregnancy, 89.3% received UFH. No maternal deaths occurred, and fetal demise occurred in 8 pregnancies (7.8%) at a median of 14 weeks of gestation. There were 2 episodes of PE (1.9%) and 2 major bleeding events requiring transfusion (1.9%).[39] UFH is cheaper than LMWH; therefore, UFH remains an efficacious anticoagulant option for pregnant women who cannot afford LMWH. Owing to the physiologic changes associated with pregnancy, LMWH and UFH dosages may need to be adjusted. An observational study of 20 pregnant women with acute VTE found no recurrent VTE or major bleeding after treatment with dalteparin; however, dalteparin doses needed to be approximately 10% to 20% higher than those recommended in nonpregnant women to obtain therapeutic anti-Xa activity.[40]

Warfarin is a teratogen and should not be used for the treatment of VTE in pregnancy. Warfarin crosses the placenta and has been associated with nasal hypoplasia, stippled epiphyses, and growth restriction, particularly between 6 and 9 weeks of gestation. Every effort should be made to avoid warfarin, particularly in the first trimester, and to substitute UFH or LMWH for warfarin between 6 and 12 weeks of gestation. The bridging process should begin early in the gestational age owing to the long half-life of warfarin.[41] Warfarin use later in gestation has been associated with fetal hemorrhage and central nervous system abnormalities. Other complications include microcephaly, blindness, deafness, fetal growth restriction, increased risk for abortion, and fetal death.[42-46] Therefore, its use in later trimesters of pregnancy is restricted to women with mechanical heart valves.

The DOACs are not approved for use in pregnancy. Although limited anecdotal reports of DOAC use in pregnancy are available, preclinical evidence exists of placental transfer with the direct Xa inhibitors rivaroxaban (Xarelto, Janssen) and apixaban (Eliquis, Bristol-Myers Squibb) and the oral thrombin inhibitor dabigatran (Pradaxa, Boehringer Ingelheim), thus increasing the risk to the fetus.[47-50] Edoxaban (Savaysa, Daiichi Sankyo), another direct Xa inhibitor, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It should be discontinued in nursing mothers as well.[51]

Thrombolysis/Thrombectomy

Fetal and maternal survival are dependent on adequate maternal perfusion and oxygenation. The risk of death from PE is significant, with a cross-sectional study of 58 patients with acute, massive PE showing a 55% mortality rate.[52] Thus, pregnancy is not an absolute contraindication to mechanical or systemic (recombinant tissue plasminogen activator or streptokinase) thrombolysis in an unstable patient at high risk for death.[53,54]

In a systematic review of 127 cases of severe PE during pregnancy or the postpartum period (83% massive; 23% with cardiac arrest), a total of 83 women received thrombolysis, and the survival rate among these women was 94% (95% CI, 86%-98%). The risk of major bleeding was 17.5% during pregnancy and 58.3% in the postpartum period, with 12.0% fetal deaths. Among 36 women with surgical thrombectomy, maternal survival was 86.1% (95% CI, 71%-95%) and the rate of major bleeding was 20.0%, with fetal deaths in 20.0%. About half of severe postpartum PEs occurred within 24 hours of delivery. In the postpartum period, given the high risk of major bleeding with thrombolysis, other therapeutic options such as surgical or catheter pulmonary embolectomy are important therapeutic and potentially life-saving options.[55]

Inferior Vena Cava Filters

Placement of an inferior vena cava (IVC) filter is indicated in patients who have an acute DVT and absolute contraindications for anticoagulation. In addition, it can be considered in patients with extensive iliofemoral venous thrombosis within 2 to 4 weeks prior to expected delivery.[56] In a systematic review of 44 studies of IVC filters placed in pregnant patients, the IVC filter complication rate was 8.87% and the failure-to-retrieve rate was 11.25%.[57] The complication rate is similar to that found in the nonpregnant population. Thus, IVC filters may be used when appropriately indicated and should be removed as soon as clinically feasible.

In another systematic review using retrievable IVC filters in 43 pregnant women, the rate of PE was 0% in the pregnant group and 0.9% in the general population. Complications that occurred more frequently in pregnancy than in the general population included thrombosis of the filter (2.3% vs 0.9%) and perforation of the IVC (7.0% vs 4.4%). Failure to retrieve the filter also was more common in pregnancy (26% vs 11%) but did not correlate with the type of device, duration of insertion, or mode of delivery. The decision to use an IVC filter in pregnancy needs careful consideration by a multidisciplinary team. The risk/benefit ratio should be individualized and discussed with the patient.[58]

Peripartum Bleeding Risk in Pregnant Women on Therapeutic Anticoagulation

The risk for bleeding with anticoagulation is considered acceptable. In a retrospective cohort study of 143

pregnancies in 88 women receiving therapeutic-dose anticoagulation, the risk of postpartum hemorrhage (PPH) after vaginal delivery (defined as estimated blood loss >500 mL) was 30% in those who received LMWH vs 18% in those who did not receive LMWH (OR, 1.9; 95% CI, 1.1-3.5). However, the risk of severe PPH after vaginal delivery (defined as estimated blood loss ≥1000 mL) was similar (5.6% vs 5.0%; OR, 1.1; 95% CI, 0.4-3.6). The risk for PPH after cesarean section was 12% in LMWH users vs 4% in nonusers (OR, 2.9; 95% CI, 0.5-19.4). Interestingly, the overall risk of PPH within 24 hours after the last injection of LMWH did not significantly differ from the risk in women who delivered more than 24 hours after the last injection. Comparing women who had a planned induction of labor vs women who had spontaneous onset of labor and delivered within 24 hours after the last dose of LMWH, the women who had a spontaneous onset of labor had a 1.9-fold increased risk for PPH vs women who had a planned induction (95% CI, 0.6-5.8; *P*=.29).[59] In clinical practice, it is common to schedule induction of labor in pregnant women who are receiving therapeutic-dose anticoagulation.

Prophylaxis

Women at high risk for pregnancy-associated VTE should receive counseling during preconception and pregnancy regarding the signs and symptoms of DVT or PE, and have a plan in place should these symptoms arise. Prophylaxis should be based on individual risk factors. There are different indications for antepartum and postpartum prophylaxis. The ACCP guidelines on antithrombotic therapy outline recommendations ranging from clinical vigilance to prophylactic-dose and intermediate-dose anticoagulation, depending on the risk for VTE recurrence, including factors such as personal and family history of VTE and type of thrombophilia (Table 3).[15,60] In general, women with a history of estrogen-related VTE, or women with single or recurrent unprovoked VTE who are not on chronic anticoagulation, should receive antepartum and postpartum pharmacologic thromboprophylaxis with either prophylactic-dose or intermediate-dose LMWH (grade 2C recommendation). In patients with a prior history of provoked VTE (non–estrogen-related), antepartum clinical vigilance and postpartum pharmacologic thromboprophylaxis are recommended (grade 2C, 2B recommendations). In asymptomatic pregnant women who are homozygote carriers for factor V Leiden or prothrombin G20210A variants and have a positive family history of thrombosis, antepartum and postpartum pharmacologic thromboprophylaxis is recommended (grade 2B recommendation). In asymptomatic homozygote carriers of factor V Leiden or prothrombin G20210A variants and antithrombin deficiency who have no family history of thrombosis, and women with all other thrombophilias with a positive family history of thrombosis, postpartum pharmacologic thromboprophylaxis is indicated (grade 2B and 2C recommendations, respectively). For women with confirmed obstetric antiphospholipid syndrome, antepartum thromboprophylaxis with a prophylactic dose of LMWH and low-dose aspirin is recommended (grade 1B recommendation). For pregnant women with all other thrombophilias who have no personal or family history of thrombosis, clinical vigilance is suggested (grade 2C recommendation).[15,38] As an alternative to LMWH, VKAs such as warfarin can be used for postpartum thromboprophylaxis with adequate bridging with LMWH until the international normalization ratio is in the therapeutic range (2.0). Bridging is initiated

Table 3. Indications for Antepartum and/or Postpartum Pharmacologic Thromboprophylaxis

Antepartum Prophylaxis	Postpartum Prophylaxis
• Single unprovoked VTE • Estrogen-related VTE • Recurrent unprovoked VTE not on long-term anticoagulation	• Any prior VTE
• Asymptomatic homozygote carriers of factor V Leiden • Asymptomatic carriers of combined thrombophilia, regardless of family history • Asymptomatic homozygote carriers of prothrombin G20210A variant, and positive family history of VTE	• Asymptomatic homozygote carriers of factor V Leiden, prothrombin G20210A variants, or combined thrombophilia, regardless of family history
• Women with antithrombin deficiency with family history of VTE	• Women with antithrombin, protein C or S deficiency, and positive family history of VTE
• Women with clinical and laboratory criteria for APS not on long-term anticoagulation	• Women with clinical and laboratory criteria for APS not on long-term anticoagulation • Asymptomatic women with confirmed high-risk profile (triple-positive) aPLs

aPLs, antiphospholipid antibodies; APS, antiphospholipid syndrome; VTE, venous thromboembolism.

Sources: Bates SM et al. *Chest*. 2012;141(2)(suppl):e691S-e736S; Bates SM et al. *Blood Adv*. 2018;2(22):3317-3359; Bates SM et al. *J Thromb Thrombolysis*. 2016;41(1):92-128.[16,38,60]

when the postpartum bleeding risk has subsided. Some guidelines suggest delaying resumption of the VKA for at least 5 days after delivery.[60] Warfarin and LMWH are safe anticoagulants to use during lactation, but no clinical data exist on the effects of the DOACs on infants during lactation. Data from animal studies indicate that DOACs are secreted into breast milk, and therefore are not recommended for breastfeeding women.

Special consideration should be made for patients with a heparin allergy. For nonpregnant patients with a history of heparin-induced thrombocytopenia, fondaparinux is often used for prophylaxis. Fondaparinux, a synthetic pentasaccharide, crosses the placenta in small quantities, but reports exist of the successful use of fondaparinux in pregnancy. In a study of 13 women (15 pregnancies), fondaparinux was initiated in 6, 8, and 1 of the pregnancies in the first, second, and third trimester, respectively. There were 10 uncomplicated pregnancies. The remaining 5 pregnancies were complicated, with miscarriage in 2; elective termination of pregnancy owing to fetal anomalies in 1; dichorionic, diamniotic twin pregnancy complicated with spontaneous rupture of membranes at 22 weeks of gestation with 1 surviving twin; and 1 pregnancy resulting in an infant born with cerebral palsy.[61] Fondaparinux may be considered in patients with severe allergy to heparins; however, multicenter studies are necessary to standardize the use of this anticoagulant in pregnancy. No published data exist on the excretion of fondaparinux into human milk, and the effects on the nursing infant are unknown. As a negatively charged oligosaccharide, only minor amounts of fondaparinux are expected to pass the intestinal epithelial barrier after oral administration, and significant absorption by the nursing infant is unlikely.[60]

In the United States, it is a common practice to switch women from a prophylactic dose of LMWH to a prophylactic dose of UFH at 36 weeks of gestation to ensure the option of neuraxial anesthesia. Controversy exists, however, regarding the optimal prophylactic dose of UFH. A prospective study of 14 pregnant women receiving UFH prophylaxis found that a dose of 5000 U twice a day was inadequate to achieve prophylactic heparin levels in any patient in the second or third trimester.[62] In a retrospective study of 25 pregnant women on intermediate-dose UFH, the mean UFH dose required to achieve a target anti–factor Xa level of 0.1 to 0.3 U/mL was 236.9 U/kg/day.[63] At the present time, prophylactic dosing recommendations for UFH are based on expert opinion.[17] It is also debatable what dose of LMWH should be administered for prophylaxis in pregnancy. Guidelines on antithrombotic therapy in pregnancy from the ACCP, the American College of Obstetricians and Gynecologists (ACOG), and the Royal College of Obstetrics and Gynaecologists (RCOG) recommend either a prophylactic dose or an intermediate dose of LMWH.[15,37,60] A prospective multicenter clinical trial called the Highlow study (Comparison of Low and Intermediate Dose Low-Molecular-Weight Heparin to Prevent Recurrent Venous Thromboembolism in Pregnancy) is currently investigating 2 doses of LMWH (low dose and intermediate dose) to determine which one is superior in preventing VTE in pregnancy.[64]

Delivery via cesarean section increases the risk for VTE by 3-fold compared with vaginal delivery. Given this risk and based on data from perioperative studies, women who deliver by cesarean section require mechanical prophylaxis with pneumatic compression devices. Pneumatic compression devices need to be placed at the time of hospital admission and used until the woman is ambulant. Early mobilization postpartum is recommended.[37] Each woman who delivers via cesarean section should be assessed for the need of pharmacologic thromboprophylaxis.

Neuraxial Anesthesia

Administration of neuraxial anesthesia during active labor while on anticoagulation increases the risk for central nervous system bleeding. Therefore, if spontaneous labor occurs in women on therapeutic-dose anticoagulation, neuraxial anesthesia cannot be used. However, in the event of elective induction of labor or caesarean section, neuraxial anesthesia may be performed 12 hours after the administration of the last prophylactic dose of LMWH or 24 hours after the last therapeutic dose of LMWH. Intravenous UFH should be stopped 6 hours before induction of labor with a confirmed normal aPTT before performing neuraxial anesthesia.[65] Neuraxial anesthesia can be administered 4 to 6 hours after the last dose of subcutaneous UFH at total doses of 10,000 U daily. If the time between the last dose of UFH is less than 4 hours, an aPTT within the normal range or an undetectable anti-Xa activity must be documented. If the dose of UFH is 7500 or 10,000 U twice a day, then an interval of a minimum of 12 hours is required prior to administration of neuraxial anesthesia. For a total daily dose of more than 20,000 U of UFH, the interval from the last dose of UFH and the neuraxial anesthesia must be at least 24 hours. The American Society of Regional Anesthesia and Pain Medicine recommends that following birth, reinitiation of prophylactic-dose LMWH should be delayed for at least 12 hours after the neuraxial block or at least 4 hours after the epidural catheter removal, whichever is greater. Therapeutic-dose LMWH should be administered no earlier than 24 hours after neuraxial anesthesia and at least 4 hours after the removal of the epidural

catheter, provided that proper hemostasis is achieved.[66] If no regional anesthesia was used, a reasonable tactic regarding time to reinitiate anticoagulation therapy with LMWH is to wait at least 6 hours after a vaginal delivery and 12 hours after a cesarean section delivery in the absence of persistent bleeding.[37] Anticoagulation with either LMWH or warfarin is recommended for at least 6 weeks postpartum.[67]

Conclusion

VTE remains a major cause of morbidity and mortality among pregnant women in the United States. It is important to recognize factors that enhance the risk for VTE. All women should be familiar with the signs and symptoms of VTE. For women with a history of VTE or thrombophilia, an anticoagulation plan should be in place. Antepartum and/or postpartum prophylaxis should be considered when appropriate, in accordance with the ACCP/ASH/ACOG guidelines. Careful attention should be paid to choosing anticoagulation therapy in pregnancy. LMWH remains the preferred option unless contraindications exist. With adequate diagnosis, identification of at-risk patients, and a multidisciplinary approach that includes high-risk obstetricians, hematologists, and anesthesiologists, we can provide optimal care for these women.

Disclosures

The authors have no relevant financial conflicts of interest.

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