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Thromboembolism in Pregnancy

Women who are pregnant or in the postpartum period have a fourfold to fivefold increased risk of thromboembolism compared with nonpregnant women (1, 2). Approximately 80% of thromboembolic events in pregnancy are venous (3), with a prevalence of 0.5–2.0 per 1,000 pregnant women (4–9). Venous thromboembolism (VTE) is one of the leading causes of maternal mortality in the United States, accounting for 9.3% of all maternal deaths (10).

The prevalence and severity of this condition during pregnancy and the peripartum period warrant special consideration of management and therapy. Such therapy includes the treatment of acute thrombotic events and prophylaxis for those at increased risk of thrombotic events. The purpose of this document is to provide information regarding the risk factors, diagnosis, management, and prevention of thromboembolism, particularly VTE in pregnancy. This Practice Bulletin has been revised to reflect updated guidance regarding screening for thromboembolism risk and management of anticoagulation around the time of delivery.

Background

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are collectively referred to as VTE. Approximately 75–80% of cases of pregnancy-associated VTE are caused by DVT, and 20–25% of cases are caused by PE (3, 7, 11). Although approximately one half of these events occur during pregnancy and one half occur during the postpartum period, the risk per day is greatest in the weeks immediately after delivery (3–8, 12).

Pregnancy-Associated Changes and Venous Thromboembolism

Pregnancy is associated with physiologic and anatomic changes that increase the risk of thromboembolism, including hypercoagulability, increased venous stasis, decreased venous outflow (13, 14), compression of the inferior vena cava and pelvic veins by the enlarging uterus (15), and decreased mobility (16–19). Pregnancy also alters the levels of coagulation factors normally responsible for hemostasis (see Table 1). The overall effect of these changes is an increased thrombogenic state. When DVT occurs during pregnancy, it is more likely to involve the left lower extremity and to be more proximal, involving the iliac and iliofemoral veins, in comparison with nonpregnant populations (20–22). This distribution has been attributed to increased venous stasis in the left leg related to compression of the left iliac vein by the right iliac artery (May–Thurner anatomy), coupled with compression of the vena cava by the gravid uterus.

Risk Factors

The risk of VTE may be higher in the third trimester compared with the first and second trimesters (2), but the increased risk of VTE is present from the first trimester (21, 22), often before many of the anatomic changes of pregnancy occur. The risk of VTE is higher during the postpartum period than it is during pregnancy, especially during the first week postpartum (1).

The most important individual risk factor for VTE in pregnancy is a personal history of thrombosis. The risk of recurrent VTE during pregnancy is increased threefold to fourfold (relative risk, 3.5; 95% CI, 1.6–7.8), and 15–25% of all cases of VTE in pregnancy are recurrent events (23).

Table 1. Changes in the Normal Functioning of the Coagulation System During Pregnancy

Coagulant Factors	Change in Pregnancy
Procoagulants	
Fibrinogen	Increased
Factor VII	Increased
Factor VIII	Increased
Factor X	Increased
Von Willebrand factor	Increased
Plasminogen activator inhibitor-1	Increased
Plasminogen activator inhibitor-2	Increased
Factor II	No change
Factor V	No change
Factor IX	No change
Anticoagulants	
Free Protein S	Decreased
Protein C	No change
Antithrombin	No change

Data from Bremme KA. Haemostatic changes in pregnancy. Best Pract Res Clin Haematol 2003;16:153–68 *and* Medcalf RL, Stasinopoulos SJ. The undecided serpin. The ins and outs of plasminogen activator inhibitor type 2. Febs J 2005;272:4858–67.

The next most important individual risk factor for VTE in pregnancy is the presence of a thrombophilia (3, 22). Thrombophilia is present in 20–50% of women who experience VTE during pregnancy and the postpartum period (24). Both acquired and inherited thrombophilias increase the risk of VTE (25–27).

Besides a personal history of thrombosis, or the presence of a thrombophilia, or both, the primary risk factors for the development of pregnancy-associated VTE are the physiologic changes that accompany pregnancy and childbirth. Cesarean delivery, particularly when complicated by postpartum hemorrhage or infection, as well as medical factors or pregnancy complications such as obesity, hypertension, autoimmune disease, heart disease, sickle cell disease, multiple gestation, and preeclampsia also increase the risk of VTE (3, 6–8, 16, 28–31). A meta-analysis regarding the risk of VTE after cesarean delivery found that cesarean was an independent risk factor for VTE, with an estimated incidence of approximately 3 cases per 1,000, a fourfold increased risk as compared with vaginal delivery (32).

Anticoagulation Medications in Pregnancy

The use of anticoagulation therapy in women during pregnancy warrants special consideration for the woman and her fetus. Risks and benefits should be discussed before the initiation of anticoagulation therapy so that women can participate in the selection of a treatment regimen that matches their preferences and values (30). Most women who require anticoagulation therapy before pregnancy will need to continue this therapy during pregnancy and the postpartum period. Common anticoagulation medications include low-molecular-weight heparin, unfractionated heparin, and warfarin. In general, the preferred anticoagulants in pregnancy are heparin compounds.

Heparin Compounds

Neither unfractionated heparin nor low-molecular-weight heparin crosses the placenta (33, 34) and both are considered safe in pregnancy (35). Unique considerations regarding the use of anticoagulation therapy in pregnancy include a 40–50% increase in maternal blood volume; an increase in glomerular filtration, which results in increased renal excretion of heparin compounds; and an increase in protein binding of heparin (36). During pregnancy, unfractionated heparin and low-molecular-weight heparin have shorter half-lives and lower peak plasma concentrations, usually necessitating higher doses and more frequent administration in order to maintain effective concentrations (37–43). When describing regimens

of unfractionated heparin or low-molecular-weight heparin, adjusted-dose unfractionated heparin or low-molecular-weight heparin refers to doses that are adjusted based on activated partial thromboplastin time (aPTT) (for unfractionated heparin) or maternal weight (low-molecular-weight heparin), whereas prophylactic or intermediate doses are prespecified based upon the medication being used (Table 2).

Because of its greater reliability and ease of administration, low-molecular-weight heparin is recommended rather than unfractionated heparin for prevention and treatment of VTE within and outside of pregnancy (30). There are few comparative studies of low-molecular-weight heparin use in pregnancy, but in nonpregnant patients low-molecular-weight heparin has been associated with fewer adverse effects than unfractionated

Table 2. Anticoagulation Regimen Definitions

Anticoagulation Regimen	Anticoagulation Dosage
Prophylactic LMWH*	Enoxaparin, 40 mg SC once daily
	Dalteparin, 5,000 units SC once daily
	Tinzaparin, 4,500 units SC once daily
	Nadroparin, 2,850 units SC once daily
Intermediate-dose LMWH	Enoxaparin, 40 mg SC every 12 hours
	Dalteparin, 5,000 units SC every 12 hours
Adjusted-dose (therapeutic) LMWH†	Enoxaparin, 1 mg/kg every 12 hours
	Dalteparin, 200 units/kg once daily
	Tinzaparin, 175 units/kg once daily
	Dalteparin, 100 units/kg every 12 hours
	Target an anti-Xa level in the therapeutic range of 0.6–1.0 units/mL 4 hours after last injection for twice-daily regimen; slightly higher doses may be needed for a once-daily regimen.
Prophylactic UFH	UFH, 5,000–7,500 units SC every 12 hours in first trimester
	UFH, 7,500–10,000 units SC every 12 hours in the second trimester
	UFH, 10,000 units SC every 12 hours in the third trimester, unless the aPTT is elevated
Adjusted-dose (therapeutic) UFH†	UFH, 10,000 units or more SC every 12 hours in doses adjusted to target aPTT in the therapeutic range (1.5–2.5 × control) 6 hours after injection
Postpartum anticoagulation	Prophylactic, intermediate, or adjusted dose LMWH for 6–8 weeks as indicated. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference.
Surveillance	Clinical vigilance and appropriate objective investigation of women with symptoms suspicious of deep vein thrombosis or pulmonary embolism. VTE risk assessment should be performed prepregnancy or early in pregnancy and repeated if complications develop, particularly those necessitating hospitalization or prolonged immobility.

Abbreviations: aPTT, activated partial thromboplastin time; INR, international normalized ratio; LMWH, low-molecular-weight heparin; SC, subcutaneously; UFH, unfractionated heparin; VTE, venous thromboembolism.

*Although at extremes of body weight, modification of dose may be required.

†Also referred to as weight adjusted, full treatment dose.

heparin (30). Potential short- and long-term advantages of low-molecular-weight heparin include fewer bleeding episodes, a more predictable therapeutic response, a lower risk of heparin-induced thrombocytopenia, a longer half-life, and less bone mineral density loss (35, 44, 45).

Importantly, neither low-molecular-weight heparin nor unfractionated heparin is associated with significant bone loss when used in prophylactic doses for the duration of pregnancy (46–48). Unfractionated heparin, which is associated with increased bruising at the injection sites, also has been associated with other skin reactions and serious allergic reactions (49). Relative disadvantages of low-molecular-weight heparin surrounding the time of delivery include its longer half-life, the inability to rapidly assess current effect with standard laboratory studies (eg, aPTT), and the inability to pharmacologically reverse its effect, which are important considerations for neuraxial anesthesia and peripartum bleeding risk.

Warfarin

Warfarin, a vitamin K antagonist commonly used for long-term anticoagulation therapy outside of pregnancy, has been associated with potentially harmful fetal effects, especially with first-trimester exposure (50–56). Warfarin embryopathy has been linked with exposure at 6–12 weeks of gestation, highlighting the importance of prepregnancy and early pregnancy care in patients using warfarin (57). Therefore, for most women receiving prolonged anticoagulation therapy who become pregnant, it is recommended that low-molecular-weight heparin be used in place of warfarin.

Although rarely prescribed in pregnancy, vitamin K antagonists such as warfarin are still considered for women with mechanical heart valves because of the high risk of thrombosis even with heparin or low-molecular-weight heparin anticoagulation therapy (58). The management of such women requires a multidisciplinary care approach, and the decision regarding optimal anticoagulation therapy merits a detailed discussion with the patients and their obstetrician–gynecologists or other health care providers regarding the risks and benefits of the various treatment options depending on the gestational age. Regimens include adjusted-dose low-molecular-weight heparin or unfractionated heparin throughout pregnancy or from the 6th week until the 13th week with substitution by vitamin K antagonists until close to delivery when low-molecular-weight heparin or unfractionated heparin is resumed (58). The risk of fetal hemorrhage in women on warfarin appears to be greatest around the time of delivery; therefore, if delivery unexpectedly occurs while a woman is receiving a vitamin K antagonist, cesarean delivery may be required and the neonate may require administration of vitamin K and fresh frozen plasma.

Oral Direct Thrombin Inhibitors and Anti-Xa Inhibitors

Oral direct thrombin inhibitors (dabigatran) and anti-Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban) should be avoided in pregnancy and lactation because there are insufficient data to evaluate safety for the woman, fetus, and breastfeeding neonate (59). Ex vivo studies of human placentas demonstrate transfer of oral direct thrombin inhibitors and anti-Xa inhibitors across the placenta, which raises concern for an indirect effect on fetal blood coagulation (60–62). Similarly, maternal ingestion of oral direct thrombin inhibitors and anti-Xa inhibitors results in detectable levels in human milk (63, 64).

The association between the use of oral direct thrombin inhibitors (dabigatran) and anti-Xa inhibitors during the first trimester of pregnancy and congenital malformations remains largely unknown. In a prospective study of 37 pregnant women inadvertently exposed to rivaroxaban, one patient had a fetus with a conotruncal cardiac defect; however, this patient also had a history of a child with a heart defect without rivaroxaban exposure (65). Until more data are available, women should be transitioned to low-molecular-weight heparin prepregnancy or as soon as possible during pregnancy.

Clinical Considerations and Recommendations

▶ ***For whom, when, and how should risk assessment for thromboembolism during pregnancy occur?***

Every obstetric patient should be asked about a personal and family history of thromboembolism. In a recent review of guidelines for the prevention of VTE in pregnancy from the United States and other international bodies, eight of the nine guidelines assessed recommended that all women should also undergo risk factor assessment for VTE either early in pregnancy or in the prepregnancy period (66). The Royal College of Obstetricians and Gynaecologists recommends that assessment be repeated at admission to the hospital or if a pregnancy complication develops (such as preeclampsia) (67). Each facility should review the available VTE risk assessment protocols and adopt and implement one of them in a systematic way to reduce the incidence of VTE in pregnancy and the postpartum period.

There are several risk assessment tools for VTE in pregnancy. In its 2015 guideline, *Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium* (67), the Royal College of Obstetricians and Gynaecologists stratifies patients antenatally and postnatally into low, intermediate, and high risk of VTE based on preexisting risk factors, obstetric risk factors, and transient risk factors. The 2012 guidelines of the American College of Chest Physicians also outline a risk assessment tool to identify women at increased risk of postpartum VTE. The National Partnership for Maternal Safety has merged and simplified the Royal College of Obstetricians and Gynaecologists' and the American College of Chest Physicians' recommendations for risk assessment (68) for use at the first prenatal visit.

No widely accepted scoring system has been prospectively validated in the obstetric population and most scoring systems have made extrapolations based on relative risk of VTE. Furthermore, it is unknown whether risk factors are additive, multiplicative, or neutral. More data from large cohorts of pregnant women and women in the postpartum period in whom risk evaluation for VTE has been obtained, which weigh the benefits, harms, and cost-effectiveness of interventions, will need to be acquired to determine the optimal risk assessment practice.

▶ *What is the evidence for thromboprophylaxis in pregnancy and the postpartum period?*

There is insufficient evidence to guide clinical decision making regarding routine pharmacologic thromboprophylaxis during and after pregnancy, highlighting the need for large-scale high quality research on the subject (69). Available evidence has been extrapolated from nonpregnant patients. Current evidence is insufficient to recommend universal adoption of pharmacologic prophylaxis for VTE, and thromboprophylaxis should be individualized according to patient risk factors. In the absence of clear, randomized, controlled trial evidence, practitioners can rely on consensus-derived clinical practice guidelines or recommendations from national and international societies (70).

▶ *How is a venous thromboembolism diagnosed in pregnancy and the postpartum period?*

Deep Vein Thrombosis

Deep venous thrombosis accounts for most cases of pregnancy-associated VTE (3, 7, 11). The two most common initial symptoms of DVT, present in more than 80% of women with pregnancy-associated DVT, are pain and swelling in an extremity (22). A difference in calf circumference of 2 cm or more is particularly suggestive of DVT in a lower extremity (71). When signs or symptoms suggest new onset DVT, the recommended initial diagnostic test is compression ultrasonography of the proximal veins (30). In contrast to the nonpregnant population, in which DVT is most commonly distal, a systematic review found a high frequency of ileofemoral (64%) and iliac (17%) thromboses in pregnant women with confirmed DVT (20).

When results are negative or equivocal and iliac vein thrombosis is suspected (based upon swelling of the entire leg, with or without flank, buttock, or back pain), additional imaging with Doppler ultrasonography of the iliac vein, venography, or magnetic resonance imaging is recommended (72, 73). Alternatively, depending on the clinical circumstances, empiric anticoagulation may be a reasonable option. When results are negative and iliac vein thrombosis is not suspected, repeat imaging in 3 days and 7 days should be considered (73).

Although measurement of D-dimer levels is a useful screening tool to exclude VTE in the nonpregnant population, pregnancy is accompanied by a progressive increase in D-dimer levels, such that a high D-dimer level does not reliably predict VTE (74–76). False negative D-dimers also have been reported in pregnant women with DVT or PE; as such, given the minimal information gained from this test, it is not recommended as part of the evaluation of VTE in pregnancy or the postpartum period (77, 78).

Pulmonary Embolism

The diagnosis of new-onset PE is similar to that in the nonpregnant individual. Ventilation–perfusion scanning and computed tomographic (CT) angiography are associated with relatively low radiation exposure for the fetus (79). Although the fetal exposure from ventilation–perfusion is low (approximately 0.32–0.64 mGy) (77), mean fetal doses associated with helical CT are lower (0.0033–0.02 mGy for the first trimester, 0.0079–0.0767 mGy for the second trimester, and 0.0513–0.1308 mGy for the third trimester). Even though fetal radiation exposure is lower with CT, both studies are associated with low radiation exposure for the fetus, and maternal radiation exposure (particularly to the breast) is lower with ventilation–perfusion scanning. The American Thoracic Society and the Society of Thoracic Radiology clinical practice guidelines for the evaluation of suspected PE in pregnancy suggest that chest X-ray be used as an initial evaluation, with progression to ventilation perfusion scan if the chest X-ray is normal and CT angiography if the chest X-ray is abnormal (77). This recommendation is based in part on the higher radiation dose to the pregnant woman with CT angiography.

However, the selection of the most appropriate test also will rely on local availability and expertise. A recent Cochrane review concluded that ventilation–perfusion scan and CT angiography were reasonable for the exclusion of PE in pregnancy, but cautioned that the quality of evidence was low and it was unclear which test was more accurate (80).

▶ *What is the appropriate evaluation of women with a prior venous thromboembolism?*

Women with a history of thrombosis who have not had a complete evaluation of possible underlying etiologies should be tested for antiphospholipid antibodies (27) and for inherited thrombophilias (26). The results of thrombophilia testing in women with a prior VTE may alter the recommendation for pharmacologic prophylaxis during pregnancy or the intensity of treatment from a prophylactic to an adjusted-dose regimen of low-molecular-weight heparin (81).

▶ *Who are candidates for anticoagulation therapy during pregnancy and the immediate postpartum period?*

Adjusted-dose anticoagulation is recommended for all women with acute VTE during pregnancy. Although a moderated intensity of anticoagulation after a full-dose treatment for 3–6 months has been shown to be safe in some patient populations, the safety of this approach in pregnancy is unknown because the provoking factor is unresolved (82). However, international consensus guidelines suggest that after initial treatment (3–6 months dependent upon the type of VTE event), anticoagulation intensity can be decreased to intermediate or prophylactic dose for the remainder of the pregnancy and for at least 6 weeks postpartum (83, 84). Other candidates for anticoagulation during pregnancy include women with a history of thrombosis or those who are at significant risk of VTE during pregnancy or the postpartum period, such as those with thrombophilias.

▶ *How should anticoagulation therapy be administered?*

There are no large trials regarding the optimal dose of anticoagulants in pregnancy, and recommendations for their use are based on case series and expert opinion. Adjusted-dose (therapeutic) anticoagulation is recommended for women with acute thromboembolism during the current pregnancy or those at high risk of thrombosis, such as women with a history of recurrent thrombosis or mechanical heart valves (30). The decisions regarding agent, dose, and length of treatment may be adjusted based on other risk factors such as cesarean delivery, prolonged immobility, obesity, obstetric complications, and personal or family history of thrombophilias and VTE (see Table 3).

Based on the pharmacokinetics of the heparin agents in pregnancy, low-molecular-weight heparin should be administered once or twice daily and subcutaneous unfractionated heparin at least every 12 hours (Table 2) (38–42). A retrospective study of once daily versus twice daily doses of various heparins for VTE in pregnancy found no cases of recurrent VTE in 126 women, 66% of whom received once daily low-molecular-weight heparin (85). Another study that compared once daily tinzaparin versus twice daily tinzaparin for the treatment of VTE in pregnancy found that a higher-than-recommended dosage was required to maintain anti-Xa activity in the target range in women who took tinzaparin only once a day (40). Another retrospective study of the once-a-day tinzaparin regimen found two unusual thrombotic complications among 37 pregnancies (86). Any adjustment for obesity is incorporated into adjusted-dose (therapeutic) regimens. Although there is no evidenced-based protocol for adjusting prophylactic doses, at extremes of body weight or as pregnancy progresses, intermediate doses of low-molecular-weight heparin may be considered (88). The required dose for prophylactic unfractionated heparin increases throughout pregnancy and weight gain and dosage adjustments have been recommended for each trimester (88, 89).

▶ *Which anticoagulants should be used in cases of heparin allergy or heparin-induced thrombocytopenia?*

The risk of heparin-induced thrombocytopenia in the obstetric population is generally estimated at less than 0.1% (90, 91). Guidelines recommend obtaining platelet counts at the initiation of anticoagulation when the risk of heparin-induced thrombocytopenia is greater than 1%; therefore, in the absence of other risk factors, most obstetric patients will not require platelet monitoring (90). In cases of severe cutaneous allergies or heparin-induced thrombocytopenia in pregnancy, consultation with a hematologist is recommended. Fondaparinux (a synthetic pentasaccharide) may be the preferred anticoagulant. Although a recent retrospective study that compared fondaparinux with enoxaparin (administered between day 6 of the menstrual cycle and continued until 12 weeks of gestation) found no untoward effects of fondaparinux on the woman or infant (92), anticoagulant activity has been detected in umbilical cord blood of exposed fetuses (93). Use of this and other parenteral direct thrombin inhibitors should be limited to those

Table 3. Recommended Pharmacologic Thromboprophylaxis in Pregnancy and the Postpartum Period

Clinical Scenario	Antepartum Management	Postpartum Management
No history of VTE, no thrombophilia	Surveillance* without anticoagulation therapy	Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has multiple risk factors.†
VTE diagnosed during pregnancy	Adjusted-dose LMWH/UFH	Adjusted-dose LMWH/UFH for a minimum of 6 weeks postpartum. Longer duration of therapy may be indicated depending on the timing of VTE during pregnancy, prior VTE history, or presence of a thrombophilia. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference.
Single provoked VTE (precipitated by a specific event such as surgery, trauma, or immobility) unrelated to estrogen or pregnancy due to a transient (resolved) risk factor, no thrombophilia	Surveillance* without anticoagulation therapy	Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has additional risk factors.†
History of single unprovoked VTE (no identified precipitating factor present; includes prior VTE in pregnancy or associated with hormonal contraception), not on long-term anticoagulation	Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH	Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH regimen for 6 weeks postpartum
Low-risk thrombophilia‡ without previous VTE	Surveillance* without anticoagulation therapy	Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has additional risks factors†
Low-risk thrombophilia‡ with a family history (first-degree relative) of VTE	Surveillance* without anticoagulation therapy or prophylactic LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
Low-risk thrombophilia‡ with a single previous episode of VTE—Not receiving long-term anticoagulation therapy	Prophylactic or intermediate-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ without previous VTE	Prophylactic or intermediate-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia§ with a single previous episode of VTE or an affected first-degree relative—Not receiving long-term anticoagulation therapy	Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH	Postpartum prophylactic anticoagulation therapy, or intermediate or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)
Two or more episodes of VTE—Not receiving long-term anticoagulation therapy (regardless of thrombophilia)	Intermediate-dose or adjusted-dose LMWH/UFH	Postpartum anticoagulation therapy with intermediate-dose or adjusted-dose LMWH/UFH for 6 weeks (therapy level should be equal to the selected antepartum treatment)
Two or more episodes of VTE—Receiving long-term anticoagulation therapy (regardless of thrombophilia)	Adjusted-dose LMWH or UFH	Resumption of long-term anticoagulation therapy. Oral anticoagulants may be considered postpartum based upon planned duration of therapy, lactation, and patient preference.

Abbreviations: LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.

*VTE risk assessment should be performed prepregnancy or early in pregnancy and repeated if complications develop, particularly those necessitating hospitalization or prolonged immobility.

†First-degree relative with a history of a thrombotic episode, or other major thrombotic risk factors (eg, obesity, prolonged immobility, cesarean delivery).

‡Low-risk thrombophilia: Factor V Leiden heterozygote; prothrombin G20210A mutation heterozygote; protein C or protein S deficiency, antiphospholipid antibody.

§High-risk thrombophilias include Factor V Leiden homozygosity, prothrombin gene G20210A mutation homozygosity, heterozygosity for factor V Leiden and prothrombin G20210A mutation, or antithrombin deficiency.

patients with severe allergic reactions to heparin. Other oral direct thrombin inhibitors (dabigatran) and anti-Xa inhibitors (rivaroxaban, apixaban, edoxaban, betrixaban) should be avoided in pregnancy and lactation (59).

▶ *How is newly diagnosed venous thromboembolism in pregnancy managed?*

Management of newly diagnosed VTE consists of initiation of adjusted-dose (therapeutic) subcutaneous low-molecular-weight heparin (30) (Table 2). Hospitalization for the initiation of anticoagulation therapy may be indicated in cases of hemodynamic instability, large clots, or maternal comorbidities. Intravenous unfractionated heparin can be considered in the initial treatment of PE and in situations in which delivery, surgery, or thrombolysis (indicated for life-threatening or limb-threatening thromboembolism) may be necessary; when patients appear to be hemodynamically stable, low-molecular-weight heparin can be substituted in anticipation of discharge from the hospital. Postpartum, these patients should receive at least 6 weeks of therapy for a minimum total duration of therapy of 3–6 months depending on the clinical scenario (30).

▶ *How should anticoagulation therapy be monitored during pregnancy?*

Data are unclear regarding optimal surveillance of anticoagulation therapy during pregnancy. When used in adjusted (therapeutic) doses determined by weight to treat or prevent VTE, it is not clear whether the dose of low-molecular-weight heparin needs to be adjusted upward. Some suggest that the dose should be adjusted as maternal weight changes during pregnancy (94). On the basis of small studies that demonstrated the need for increased low-molecular-weight heparin to maintain antifactor Xa levels between 0.6 units/mL and 1.0 units/mL, some advocate periodic measurement of antifactor Xa levels 4–6 hours after injection, but other studies have shown that few women actually require increased doses when weight-based doses are used (30). If patients are converted from adjusted-dose low-molecular-weight heparin to a subcutaneous adjusted-dose of unfractionated heparin in anticipation of delivery, an aPTT should be checked and their dose of heparin adjusted to maintain the aPTT in the therapeutic range (goal of aPTT of 1.5–2.5 times control, 6 hours after injection).

Patients receiving prophylactic anticoagulation generally do not require monitoring because the optimal antifactor Xa levels during low-molecular-weight heparin prophylaxis in pregnancy have not been determined. Retrospective studies have suggested that measuring antifactor Xa levels may be considered in situations in which prophylaxis levels outside of the recommended range are clinically suspected, such as in the case of obesity (43, 95).

▶ *How is anticoagulation therapy managed around the time of delivery?*

Decisions regarding delivery timing should be based on the usual obstetric indications, incorporating the goals of maintaining adequate anticoagulation before delivery as well as avoiding an unwanted coagulation effect during delivery, along with patient preference. The Society for Obstetric Anesthesia and Perinatology has published consensus guidelines that address thromboprophylaxis and neuraxial anesthetic considerations specifically in the obstetric population (96). In addition to making specific management recommendations, the society recommends that every unit should have a protocol for when pregnant women and postpartum women should have anticoagulant medications held and when women who are receiving thromboprophylaxis are eligible for neuraxial anesthesia.

For women who are receiving prophylactic low-molecular-weight heparin, discontinuation is recommended at least 12 hours before scheduled induction of labor or cesarean delivery; a 24-hour interval is recommended for patients on an adjusted-dose regimen (Table 4) (96). For unfractionated heparin doses of 7,500 units subcutaneously twice a day or more, a 12-hour interval as well as evaluation of coagulation status with laboratory testing are recommended. Women receiving anticoagulation therapy may be converted from low-molecular-weight heparin to the shorter half-life unfractionated heparin in anticipation of delivery, depending upon the institution's protocol. An alternative option may be to stop anticoagulation and induce labor within 24 hours, if clinically appropriate. If conversion to unfractionated heparin is planned, timing for this should be based upon the clinical scenario, including incorporation of the likelihood of spontaneous labor and the goal of minimizing the time that appropriate anticoagulation is not being administered. Given the potential need for urgent or emergent procedures in obstetrics, the Society for Obstetric Anesthesia and Perinatology's guidelines incorporate decision support to provide guidance regarding the use of neuraxial anesthesia if the recommended time since the last dose has not elapsed (96).

The purpose of conversion to unfractionated heparin has less to do with any risk of maternal bleeding at the time of delivery, but rather the risk of an epidural or spinal hematoma with regional anesthesia; this risk, with or without altered hemostasis, is very difficult to determine, although the incidence may be approximately

Table 4. Timing of Neuraxial Anesthesia in Relation to Pharmacologic Anticoagulation

Dosage Regimen	Intrapartum, Elective Procedure	Intrapartum, Urgent/ Emergent Procedure	Postpartum
UFH prophylaxis (7,500 units SC twice daily or 10,000 units SC twice daily)	Hold dose for 12 hours and assess coagulation status before administering neuraxial anesthesia	Hold dose for 12 hours and assess coagulation status before administering neuraxial anesthesia. However, in urgent cases with greater competing risks from general anesthesia, placement of neuraxial anesthesia may be appropriate	Wait at least 1 hour after neuraxial blockade and catheter removal before restarting heparin
UFH adjusted-dose (>10,000 units per dose or >20,000 units per day)	Hold dose for 24 hours and assess coagulation status before administering neuraxial anesthesia	If at least 24 hours since last dose and aPTT within normal limits or undetectable anti-Xa, likely low risk for neuraxial blockade	Wait at least 1 hour after neuraxial blockade or catheter removal before restarting heparin
Low-dose LMWH prophylaxis	Wait 12 hours after last dose before neuraxial blockade	Insufficient data to make a recommendation for placement of neuraxial blockade less than 12 hours from last dose of LMWH. In high risk situations in which intervention is needed, risks of general anesthesia may outweigh risks of spinal epidural hematoma	Wait at least 12 hours after neuraxial blockade and at least 4 hours after catheter removal to restart LMWH prophylaxis
LMWH intermediate-dose or adjusted-dose	Wait 24 hours after last dose before neuraxial blockade	If less than 24 hours, insufficient evidence to recommend proceeding with neuraxial blockade	Consider waiting at least 24 hours after neuraxial blockade *and* at least 4 hours after catheter removal to restart LMWH anticoagulation

Abbreviations: LMWH, low-molecular-weight heparin; SC, subcutaneously; UFH, unfractionated heparin.

Data from Leffert L, Butwick A, Carvalho B, Arendt K, Bates SM, Friedman A, et al. The Society for Obstetric Anesthesia and Perinatology consensus statement on the anesthetic management of pregnant and postpartum women receiving thromboprophylaxis or higher dose anticoagulants. Members of the SOAP VTE Taskforce. Anesth Analg 2018;126:928–44.

3–4:1,000,000 (96). To date, there have been no published cases of spinal hematoma in parturients associated with antithrombotic therapy (with or without neuraxial block) (97). Therefore, in the absence of large series of neuraxial techniques in the pregnant population receiving prophylaxis or treatment of VTE, recommendations derived mainly from surgical patients, applied to parturients, have been integrated into the American Society of Regional Anesthesia and Pain Medicine guidelines as well as the Society for Obstetric Anesthesia and Perinatology guidelines.

Protamine sulfate can be used to reverse unfractionated heparin or, less predictably, low-molecular-weight heparin. The dose of protamine sulfate is dependent on whether the patient is receiving unfractionated heparin or low-molecular-weight heparin and the route by which these medications are being administered. Reversal of heparin, however, is rarely required and is not indicated with a prophylactic dose of heparin. For women in whom anticoagulation therapy has temporarily been discontinued, pneumatic compression devices are recommended.

▶ *What prophylaxis for venous thromboembolism is advised for patients undergoing cesarean delivery?*

Cesarean delivery approximately quadruples the risk of VTE in comparison with vaginal delivery, but in the otherwise normal patient, this risk is still low (approximately 3 per 1,000 patients) (32). Given this increased risk, and based on extrapolation from perioperative data, placement of pneumatic compression devices before cesarean delivery is recommended for all women, and early mobilization is advised after cesarean delivery (30). Pneumatic compression devices should be left in place until the patient is ambulatory.

A review of guidelines for the prevention of pregnancy-related VTE from the United States and international organizations showed considerable variation in regard to recommendations for preventing VTE after cesarean delivery (59). Each facility should carefully consider the risk assessment protocols available and adopt and implement one of them in a systematic way to reduce the incidence of VTE in pregnancy and the postpartum period (68). For patients undergoing cesarean delivery with additional risk factors for thromboembolism, individual risk assessment may support thromboprophylaxis with pneumatic compression devices and low-molecular-weight heparin (30). In those with contraindications to anticoagulants, postpartum mechanical prophylaxis is advised over no prophylaxis (30).

For women at particularly high risk of thrombosis at the time of delivery, prophylactic low-molecular-weight heparin can be combined with mechanical prophylaxis (30). For selected high-risk patients in whom significant risk factors persist after delivery, prophylaxis (at least 6 weeks after delivery) is recommended after discharge from the hospital (98, 99). Most patients who receive thromboprophylaxis during pregnancy will benefit from postpartum thromboprophylaxis, but the dose, route, and duration will vary by indication (Table 2).

Women with a very high risk of recurrent VTE (ie, proximal DVT or PE in the 2–4 weeks before delivery, particularly if this is a recurrent VTE despite adequate anticoagulation) may be candidates for placement of a retrievable vena caval filter, with removal postpartum (100, 101). However, the indications for this are limited and must be balanced against the risk of complications, including filter migration and inferior vena cava perforation, which may be increased in pregnancy (30).

▶ *When is the optimal time to resume anticoagulation therapy postpartum?*

The optimal time to restart anticoagulation therapy postpartum is unclear. A reasonable approach to minimize postpartum bleeding complications is resumption of anticoagulation therapy no sooner than 4–6 hours after vaginal delivery or 6–12 hours after cesarean delivery (Table 4). One study compared 95 women treated with peripartum enoxaparin with 303 controls and found no significant increase in the rate of severe postpartum hemorrhage when enoxaparin was restarted between 5 hours and 24 hours after a vaginal delivery and between 12 hours and 36 hours after a cesarean delivery (102). Considering delaying initiation of therapeutic anticoagulation with low-molecular-weight heparin for at least 24 hours after neuraxial blockade and 4 hours after catheter removal is recommended in the Society for Obstetric Anesthesia and Perinatology consensus statement; if therapeutic anticoagulation is desired more rapidly after delivery, intravenous heparin may be an alternative (96). When reinstitution of anticoagulation therapy is planned postpartum, pneumatic compression devices should be left in place until the patient is ambulatory and until anticoagulation therapy is restarted.

▶ *How should anticoagulation be managed postpartum?*

Women who require more than 6 weeks of postpartum anticoagulation therapy may be bridged to warfarin (103–105) or a direct oral anticoagulant if not breastfeeding. To avoid paradoxical thrombosis and skin necrosis from the early antiprotein C effect of warfarin, women who will be treated with warfarin should be bridged with adjusted-dose low-molecular-weight heparin or unfractionated heparin until an international normalized ratio in the therapeutic range (2.0–3.0) is achieved for 2 consecutive days. Warfarin can be started concurrently with adjusted-dose heparin compounds in the postpartum period. For women with mechanical heart valves, warfarin can be resumed 24 hours after delivery, with overlapping intravenous unfractionated heparin (or low-molecular-weight heparin) until therapeutic on warfarin. For patients without mechanical heart valves who require more than 6 weeks of anticoagulation, they can be switched to their oral anticoagulant when the risk of postpartum bleeding has subsided (usually 1–2 weeks). The initial dose of warfarin is 5 mg daily for 2 days, with subsequent doses determined by monitoring the international normalized ratio. For women who require only 6 weeks of anticoagulation therapy postpartum, the utility of warfarin is limited because it frequently requires 1–2 weeks of administration before a target range is attained. Consequently, many patients opt to continue low-molecular-weight heparin for the 6-week period. Because warfarin, low-molecular-weight heparin, and unfractionated heparin do not accumulate in breast milk and do not induce an anticoagulant effect in the infant, these anticoagulants are compatible with breastfeeding (103, 106, 107).

Summary of Recommendations and Conclusions

The following recommendation is based on good and consistent scientific evidence (Level A):

- When signs or symptoms suggest new onset DVT, the recommended initial diagnostic test is compression ultrasonography of the proximal veins.

The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B):

- In general, the preferred anticoagulants in pregnancy are heparin compounds.
- Because of its greater reliability and ease of administration, low-molecular-weight heparin is recommended rather than unfractionated heparin for prevention and treatment of VTE within and outside of pregnancy.
- A reasonable approach to minimize postpartum bleeding complications is resumption of anticoagulation therapy no sooner than 4–6 hours after vaginal delivery or 6–12 hours after cesarean delivery.
- Because warfarin, low-molecular-weight heparin, and unfractionated heparin do not accumulate in breast milk and do not induce an anticoagulant effect in the infant, these anticoagulants are compatible with breastfeeding.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- Women with a history of thrombosis who have not had a complete evaluation of possible underlying etiologies should be tested for antiphospholipid antibodies and for inherited thrombophilias.
- Adjusted-dose (therapeutic) anticoagulation is recommended for women with acute thromboembolism during the current pregnancy or those at high risk of thrombosis, such as women with a history of recurrent thrombosis or mechanical heart valves.
- When reinstitution of anticoagulation therapy is planned postpartum, pneumatic compression devices should be left in place until the patient is ambulatory and until anticoagulation therapy is restarted.
- Every unit should have a protocol for when pregnant women and postpartum women should have anticoagulant medications held and when women who are receiving thromboprophylaxis are eligible for neuraxial anesthesia.
- Women receiving anticoagulation therapy may be converted from low-molecular-weight heparin to the shorter half-life unfractionated heparin in anticipation of delivery, depending upon the institution's protocol.
- For women who are receiving prophylactic low-molecular-weight heparin, discontinuation is recommended at least 12 hours before scheduled induction of labor or cesarean delivery; a 24-hour interval is recommended for patients on an adjusted-dose regimen.
- Placement of pneumatic compression devices before cesarean delivery is recommended for all women, and early mobilization is advised after cesarean delivery.
- Each facility should carefully consider the risk assessment protocols available and adopt and implement one of them in a systematic way to reduce the incidence of VTE in pregnancy and the postpartum period.

For More Information

The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for ob-gyns, other health care providers, and patients. You may view these resources at www.acog.org/More-Info/ThromboembolismInPregnancy.

These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists' endorsement of the organization, the organization's website, or the content of the resource. The resources may change without notice.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and March 2018. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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