Guidance for Management of Peripartum VTE Prophylaxis

This document serves to assist in the approach to management. Each case must be handled on an individual basis, and should be replaced by clinical judgment when necessary.

Background: Pregnancy-associated VTE is a leading cause of maternal morbidity and mortality.[1] The prevalence and severity of this condition warrants special consideration of those at increased risk.[1] This document summarizes VTE prophylaxis recommendations in pregnancy, based upon the most up to date guidelines and resources. As there is some variance between guidelines regarding antepartum and postpartum management, the below summary is an attempt by the authors to create a consensus document for practical clinical use.

TABLE 1 – Anticoagulation Regimen Definitions[1]

Prophylactic Low Molecular Weight Heparin (LMWH)*	• Enoxaparin, 40mg subcutaneously (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, 40mg SC every 12 hours • Dalteparin, 5,000 units SC every 12 hours
Adjusted-dose (therapeutic) LMWH	• Enoxaparin, 1mg/kg SC every 12 hours • Dalteparin, 200units/kg SC once daily • Tinzaparin, 175 units/kg SC once daily • Dalteparin, 100 units/kg SC 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 once daily regimen
Prophylactic Unfractionated Heparin (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 second trimester • UFH, 10,000 units SC every 12 hours in the third trimester, unless the activated partial thromboplastin time (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 (1.5-2.5x 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. Venous thromboembolism (VTE) risk assessment should be performed pre-pregnancy or early in pregnancy and repeated if complications develop, particularly those necessitating hospitalization or prolonged immobility

*At extremes of body weight, dose modification may be required; 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. Furthermore, no routine monitoring required (optimal anti-Xa levels for prophylaxis in pregnancy) have been determined. Obtaining platelet counts at the initiation of anticoagulation when the risk of heparin-induced thrombocytopenia is >1% is recommended. Lastly, in most instances, warfarin and direct oral anticoagulants should NOT be used during pregnancy.[1]

TABLE 2 – Indications and Associated Anticoagulation Recommendations for Antepartum VTE Prophylaxis[1-3]

No history of VTE, no thrombophilia		Surveillance without anticoagulation therapy
Single provoked VTE (precipitated by a specific event such as surgery, trauma, or immobility) unrelated to estrogen or pregnancy due to transient risk factor, no thrombophilia		Surveillance without anticoagulation therapy
History of single unprovoked VTE		Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH regimen
History of VTE associated with pregnancy or other hormonal risk factor		Prophylactic, intermediate-dose, or adjusted dose LMWH/UFH
Low risk thrombophilia (factor V Leiden heterozygosity; prothrombin G20210A mutation heterozygosity; protein C or protein S deficiency; antiphospholipid antibody) plus <u>one</u> of the following:	A. Single previous VTE B. Family history of VTE in first degree relative	A. For single previous VTE: Prophylactic or intermediate-dose LMWH/UFH B. Family history of VTE in first degree relative: Surveillance without anticoagulation therapy or prophylactic LMWH/UFH
High-risk thrombophilia (factor V Leiden homozygosity; prothrombin G20210A mutation homozygosity; factor V Leiden heterozygosity and concurrent prothrombin G20210A mutation; antithrombin deficiency) plus <u>one</u> of the following:	A. No history of VTE B. Single previous VTE C. Family history of VTE in first degree relative	A. No history of previous VTE: prophylactic or intermediate-dose LMWH/UFH B. Single previous VTE: prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH C. Family history of VTE in first degree relative: prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH
History of 2 or more episodes of VTE and NOT on long term anticoagulation		Intermediate-dose or adjusted-dose LMWH/UFH
Immobilization with pre-pregnancy BMI of 25kg/m2 or 25kg/m2 with significant co-morbidity (systemic lupus erythematosus, sickle cell, heart disease)		Intermediate-dose or adjusted-dose LMWH/UFH
Women undergoing assisted reproductive therapy who develop severe ovarian hyperstimulation syndrome		Prophylactic LMWH

Abbreviations: VTE (venous thromboembolism); LMWH (low molecular weight heparin); SC (subcutaneous); UFH (unfractionated heparin); DOAC (direct-acting oral anticoagulant, e.g. apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban)

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TABLE 3 – Time to discontinuation of prophylactic anticoagulation *prior to delivery*

LMWH^	Low dose: 12 hrs.[1-4] Intermediate dose (40mg SC Q12h): 24 hrs.[2,4]
SC UFH^#+	Low dose: 4–6 hrs.[4] Intermediate dose: 12 hrs.[2,4] High dose: 24 hrs.[2,4]

^ For those who do not have a planned delivery, advise patient to discontinue anticoagulant at first signs of labor
# Assess coagulation status and CBC before administering neuraxial anesthesia
+ Protamine sulfate can be used to reverse therapeutic doses of UFH in emergent cases, but is NOT indicated for prophylactic doses

TABLE 4 – Optimal time to resumption of *postpartum* prophylactic anticoagulation

LMWH[$]	Vaginal delivery: no sooner than 4-6 hrs. post-delivery[2,3] Cesarean delivery: no sooner than 6-12 hrs. post-delivery[2,3] Neuraxial blockade/catheter removal: No sooner than 12 hrs. after neuraxial blockade or 4 hrs. after catheter removal (whichever is longer)[2,4]
UFH (SC)[$]	Vaginal delivery: no sooner than 4-6 hrs. post-delivery[2] Cesarean delivery: no sooner than 6-12 hrs. post-delivery[2] Neuraxial blockade/catheter removal: No sooner than 1 hr. after neuraxial blockade or 4 hrs. after catheter removal (whichever is longer)[2,4]

$ Depending on postpartum hemostasis and the indication for the anticoagulant, anticoagulation can be restarted 12 to 24 hrs. postpartum, assuming hemostasis has been achieved and no hemorrhage

Table 5 – Indications and Associated Anticoagulation Recommendations for Postpartum VTE Prophylaxis[1,2]

(The listed indications and treatments apply to patients NOT receiving long-term therapeutic anticoagulation at presentation)

No history of VTE, no thrombophilia		Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has multiple risk factors (first degree relative with a history of a thrombotic episode, or other major thrombotic risk factors [e.g. obesity, prolonged immobility, cesarean delivery])
Single provoked VTE (precipitated by a specific event such as surgery, trauma, or immobility) unrelated to estrogen or pregnancy due to transient risk factor, no thrombophilia		Surveillance without anticoagulation therapy or postpartum prophylactic anticoagulation therapy if the patient has additional risk factors (first degree relative with a history of a thrombotic episode, or other major thrombotic risk factors [e.g. obesity, prolonged immobility, cesarean delivery])
History of single unprovoked VTE		Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH regimen for 6 weeks postpartum
History of VTE associated with pregnancy or other hormonal risk factor		Prophylactic, intermediate-dose, or adjusted dose LMWH/UFH regimen for 6 weeks postpartum
Low risk thrombophilia (factor V Leiden heterozygosity; prothrombin G20210A mutation heterozygosity; protein C or protein S deficiency; antiphospholipid antibody) plus <u>one</u> of the following:	**A. Single previous VTE** **B. Family history of VTE in first degree relative**	A. Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH B. Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH
High-risk thrombophilia (factor V Leiden homozygosity; prothrombin G20210A mutation homozygosity; factor V Leiden heterozygosity and concurrent prothrombin G20210A mutation; antithrombin deficiency) plus <u>one</u> of the following:	**A. No history of VTE** **B. Single previous VTE** **C. Family history of VTE in first degree relative**	A. No history of VTE: Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH B. Single previous VTE: Postpartum prophylactic anticoagulation therapy or intermediate-dose LMWH/UFH for 6 weeks C. Family history of VTE in first degree relative: prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH for 6 weeks
History of 2 or more episodes of VTE and NOT on long term anticoagulation		Postpartum anticoagulation therapy with intermediate-dose or adjusted-dose LMWH/UFH for 6 weeks
Immobilization with pre-pregnancy BMI of 25kg/m2 or 25kg/m2 with significant co-morbidity (systemic lupus erythematosus, sickle cell, heart disease)		Consideration should be given to providing postpartum prophylaxis while in hospital to women with a history of antepartum immobilization for at least 7 days and to those who are immobilized postpartum who have a known thrombophilia or significant comorbidity
Cesarean delivery with risk factor (prior VTE, antepartum immobilization; postpartum infection; postpartum hemorrhage; pre-eclampsia with growth restriction; significant medical co-morbidities) or (or with emergency cesarean) medical conditions (postpartum hemorrhage; body mass index >30kg/m2; fetal growth restriction; pre-eclampsia; multiple pregnancy, tobacco use during pregnancy)		Prophylactic, intermediate-dose, or adjusted-dose LMWH/UFH regimen for 6 weeks postpartum

TABLE 6 – Anticoagulation compatibility with breastfeeding

Compatible with breastfeeding	LMWH, UFH, warfarin, fondaparinux[1-3]
NOT compatible or not recommended with breastfeeding	DOACs (apixaban, betrixaban, dabigatran, edoxaban, rivaroxaban)[1-3]

References:
1. Bates SM, Middeldorp S, Rodger M, et al. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis 2016;41:92-128.
2. Bates, S. M., Rajasekhar, A., Middeldorp, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Advances 2018;2,3317-3359.
3. James A, Birsner M, Kaimal A. ACOG Practice Bulletin No. 196: Thromboembolism in Pregnancy. Obstetrics & Gynecology 2018;132:e1-e17.
4. Leffert L, 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 Anesth Analg 2018;126:928-944.

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