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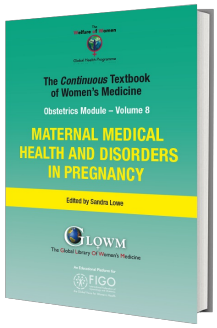

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Chapter

Prevention of Thromboembolic Disease and Thrombophilias in Pregnancy

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AUTHORS

Paul S Gibson, MD, FRCPC
Associate Professor of Medicine and Obstetrics & Gynecology, University of Calgary, Calgary, Alberta, Canada

INTRODUCTION

Pregnancy is a state of heightened coagulability, leading to an increased risk for venous thromboembolism (VTE). Virchow's triad of factors predisposing to thrombosis – hypercoagulability, venous stasis and vascular damage – all occur in pregnancy (Table 1). Venous pooling and reduced blood flow is caused by progesterone-mediated venous dilation, which is enhanced by compression of the inferior vena cava by the gravid uterus in the second half of pregnancy. The use of restricted activity or bedrest for pregnancy complications (such as threatened preterm labor or hypertension) leads to even greater risk.

Table 1 Factors that increase thrombotic risk in pregnancy

Increased maternal clotting factors • fibrinogen and factors II, VII, VIII, X and XII Reduction in maternal levels of Protein S Impaired fibrinolysis • plasminogen activator inhibitor (PAI-1) derived from the uterine decidua Venous stasis and blood pooling	Excessive elevation of pregnancy hormones • ovarian hyperstimulation syndrome, multiple gestation Other maternal/pregnancy risk factors • prior VTE • family history of VTE in a 1st-degree relative • age >35 years • obesity (BMI ≥30 pre-pregnancy) • smoking • long distance travel

• progesterone-mediated venous dilation • compression of the IVC by the gravid uterus in later pregnancy Endothelial disruption of the pelvic vessels • cesarean section Thrombophilias • high-risk: homozygous factor V Leiden or prothrombin gene mutations, antithrombin deficiency, combined thrombophilias, APLA syndrome (prior VTE) • low-risk: heterozygous factor V Leiden or prothrombin gene mutations, protein C or S deficiency, persistent APLAs (without prior VTE) Acquired antithrombin deficiency • high-proteinuric states such as nephrotic syndrome or pre-eclampsia	• use of assisted reproduction techniques, particularly if severe ovarian hyperstimulation syndrome occurs • maternal medical conditions: ◦ gross varicose veins ◦ inflammatory bowel disease ◦ infection ◦ heart disease ◦ autoimmune disease ◦ sickle cell disease ◦ active malignancy ◦ any condition necessitating the placement of a chronic indwelling IV catheter • pregnancy conditions: ◦ multiple gestation, ◦ parity ≥3, ◦ hyperemesis gravidarum, ◦ pre-eclampsia ◦ IUGR, ◦ delivery <37 weeks' gestation ◦ stillbirth ◦ prolonged labor (>24 h) ◦ mid-cavity or rotational operative delivery ◦ postpartum infection or hemorrhage >1 L ◦ immobilization/bedrest ≥7 days or surgery during pregnancy ◦ cesarean delivery (especially emergency cesarean section labor)

APLA, antiphospholipid antibody; VTE, venous thromboembolism; BMI, body mass index; IUGR, intrauterine growth restriction.

In addition, the maternal coagulation system changes during pregnancy to reduce bleeding risk, leading to hypercoagulability. Clotting factors including fibrinogen and factors II, VII, VIII, X, and XII increase substantially over the course of gestation, while the intrinsic anticoagulant protein S decreases in normal pregnancy. Impaired fibrinolysis is also in part due to increased levels of plasminogen activator inhibitor (PAI-1) derived from the uterine decidua. Acquired antithrombin deficiency may also occur in the setting of nephrotic syndrome or pre-eclampsia. These hemostatic alterations combine to reduce the risk of a serious maternal peripartum hemorrhage, but at the cost of a substantially increased risk of thrombotic complications during pregnancy and postpartum.

Finally, endothelial disruption of the pelvic veins may occur at the time of normal delivery, or particularly in the event of cesarean section.

Some women may also have underlying hypercoagulability due to inherited or acquired thrombophilic states,[1] while others have or acquire additional clinical risk factors for VTE during pregnancy/postpartum, such as age over 35, smoking, elevated BMI, cardiac/circulatory disease, use of assisted reproduction, multiple gestation, immobilization, pre-eclampsia, IUGR, cesarean delivery, peripartum/puerperal infection or postpartum hemorrhage (Table 1).[2,3,4,5] Multiple such risk factors may significantly increase an individual's risk of venous thromboembolism during pregnancy or postpartum.

Given these multiple prothrombotic tendencies, it is not surprising that pregnant women have a 5–10 fold higher risk of

thrombotic complications than similar non-pregnant women – with an absolute risk of ~1.2–1.7 per 1000 pregnancies.[5,6,7]. The timing of VTE events in pregnancy includes a relatively equal distribution of events between the antepartum weeks and postpartum – with a slight preponderance of antepartum VTE events for the third trimester[6] and a predilection of DVTs for the left leg.[8] Postpartum VTE events are clustered within the first 2–6 weeks postpartum[9,10] – making this the highest risk period for pregnancy-associated VTE events, and thus an ideal period for targeted thromboprophylaxis of high-risk women.

Who should and shouldn't have thrombophilia testing

Although thrombophilias are prevalent (~15% of the general population, variable according to genetic ancestry)[11] and may confer an increased risk of venous thromboembolism, there has been a trend away from thrombophilia testing in recent years. The decision on whether or not to undertake thrombophilia testing among patients who have experienced a VTE event is complicated by the fact that "available data (from the general population) show no significant differences in rates of recurrent VTE between patients with and those without thrombophilia or between patients who undergo testing for inherited thrombophilia and those who do not".[12] Clinical practice guidelines do not provide a standardized approach, but the general consensus is that thrombophilia testing should only be pursued if it will significantly affect clinical decision making.

Hereditary thrombophilias (Table 2) which are commonly tested for include:[11]

1. Factor V Leiden mutation (may be heterozygous or homozygous);
2. Prothrombin gene (G20210A) mutation (may be heterozygous or homozygous);
3. Protein C deficiency;
4. Protein S deficiency;
5. Antithrombin deficiency.

Table 2 Hereditary thrombophilias and VTE risk in pregnancy. Adapted from ASH Practice Guideline [13] and ACOG Practice Bulletin.[13]

Thrombophilia	Prevalence in general population	Risk of *primary* VTE in pregnancy (+ FH)	Risk of *recurrent* VTE in pregnancy
Factor V Leiden mutation			
– heterozygous	up to 15%	0.5% (0.06–1.21)	**10%**
– homozygous	<1%	**6.86% (1.0–15.9)**	**17%**
Prothrombin gene mutation			
– heterozygous	2–5%	0% (0.0–0.73)	**>10%**
– homozygous	<1%	**1.6%**	
Factor V Leiden and prothrombin gene mutations (compound-heterozygous)	0.01%	**2.82%**	**>20%**
Protein C deficiency	0.2–0.4%	1.63% (0.0–5.0)	**4–17%**
Protein S deficiency	0.03–0.13%	0% (0.0–1.46)	**Up to 22%**
Antithrombin deficiency	0.02%	**2.7%** (0.0–0.8.5)	**40%**

+FH, family history of venous thromboembolism.

In addition, the persistent presence of the antiphospholipid antibodies (APLAs) constitutes an acquired thrombophilia which may be associated with an enhanced risk of venous thromboembolism as well as an increased risk of adverse pregnancy outcomes.[14] The APLAs of significance are:

1. Lupus anticoagulant/inhibitor;
2. Anticardiolipin antibodies (moderate-high titer, IgG or IgM);
3. Anti-beta-2-glycoprotein-I (moderate-high titer, IgG or IgM);

In contrast to the general population, pregnancy planning is a situation in which thrombophilia testing may sometimes provide clinically useful information. An observational study of pregnant women with prior VTE found a 4.8% overall rate of recurrent VTE – with a much higher (16%) rate of VTE recurrence during pregnancy/postpartum among subjects with an underlying thrombophilia. Other studies have confirmed a high (>10%) rate of VTE recurrence among thrombophilic women who became pregnant.[15] In contrast, a low-risk subgroup of women was also identified: those with a temporary risk factor at the time of their primary VTE event and without a detectable thrombophilia, among whom there were no recurrent VTE events.[16] This finding suggests that thrombophilia testing may differentiate women who are at substantial risk of recurrent thrombotic events during a subsequent pregnancy (i.e. prior VTE and thrombophilia-positive) from those who may be in a 'low risk' group (prior provoked VTE with no additional/persistent VTE risk factors and thrombophilia-negative). Contemporary clinical practice guidelines (such as the recent American Society of Hematology recommendations for pregnancy[17]) do not specifically outline which circumstances merit thrombophilia testing – but the Society of Obstetricians and Gynecologists of Canada (SOGC) state that "screening for thrombophilia[s] … should [only] be done if the result will modify management in the current pregnancy".[16] This is mainly relevant in women considering pregnancy who have a prior history of 'provoked' VTE in whom the original 'secondary' factor was NOT estrogen VTE – and in whom the need for thromboprophylaxis is unclear. In this subset of women – particularly those with a minor precipitant for their initial VTE or a family history of VTE – determining the presence or absence of a thrombophilia may significantly alter their risk and therefore their management plan (see 'Who Needs Thromboprophylaxis in Pregnancy? below).

WHO NEEDS THROMBOPROPHYLAXIS IN PREGNANCY?

Although the threshold of VTE risk which justifies the antepartum use of low-molecular-weight heparin to reduce thrombotic risk is unclear, most practitioners would agree that women with a VTE risk greater than 1% should be considered for antepartum (and postpartum) thromboprophylaxis. This enhanced degree of risk is approximately ten-times greater than the baseline risk of pregnancy-associated VTE (of ~1.2 per 1000).[6]

Women with any prior venous thromboembolic event with a recognized thrombophilia

Given that pregnancy is a prothrombotic state, it is not surprising that women with a prior history of VTE have an increased risk of recurrent thrombotic events in subsequent pregnancies.[18,19] A recent systematic review of VTE among women with prior VTE identified a rate of recurrent VTE in subsequent pregnancy of 4.27%.[6] The presence of an underlying thrombophilia further increases the risk of recurrent pregnancy-associated VTE. In the cohort study described above,[16] women with prior VTE who had a known/detectable thrombophilia had a significantly higher risk of recurrent VTE in pregnancy (>10%). Even among women with a prior 'provoked' VTE event, the recurrence risk in pregnancy was >10% when they harbored a thrombophilia. Other studies have confirmed a high recurrence rate of VTE among thrombophilic women who became pregnant.[15] Based on this high risk (Table 2), most contemporary clinical practice guidelines (Table 3 and 4) concur that women with:

- any prior VTE and a known thrombophilia should receive thromboprophylaxis with LMWH throughout pregnancy and for ~6 weeks postpartum
- any thrombophilia with prior venous or arterial thrombotic events on prepregnancy anticoagulation, should be continued (in the form of therapeutic-dose LMWH) during pregnancy with a switch back to oral anticoagulation with warfarin

postpartum.[20]

- antiphospholipid antibody (APLA) syndrome with prior venous or arterial thrombotic events on prepregnancy anticoagulation, should be continued (in the form of therapeutic-dose LMWH) during pregnancy along with the addition of low-dose aspirin (81–162 mg) with a switch back to oral anticoagulation with warfarin postpartum.[20]

Table 3 Indications for thromboprophylaxis in pregnancy and postpartum.

Clinical situation	***Recommended therapy (see Table 5)***
Prior venous thromboembolism (secondary prevention)	
• Prior recurrent VTE, on long-term anticoagulation	Therapeutic LMWH (resume oral anticoagulation PP)
• Prior VTE and thrombophilia • Prior idiopathic VTE • Prior VTE associated with estrogen (combined OCP, topical estrogen or prior pregnancy)	Prophylactic LMWH, plus postpartum prophylaxis
• Prior "secondary" VTE, no known thrombophilia, no additional maternal/pregnancy risk factors	Clinical surveillance antepartum *plus* postpartum prophylaxis
Thrombophilia, no prior VTE (primary prevention)	
High risk thrombophilia • Antithrombin (AT) deficiency • Homozygous factor V Leiden • Homozygous prothrombin gene mutation • Combined thrombophilias	Prophylactic LMWH, *plus* postpartum prophylaxis Women with AT deficiency are 'heparin-resistant' and should receive therapeutic-intensity LMWH
Other thrombophilias • Heterozygous factor V Leiden or prothrombin 20210A gene mutation • Protein C or S deficiency • Persistent APLAs (lupus inhibitor or mod-high titer anticardiolipin or anti-beta-2-glycoprotein-I antibodies)	Clinical surveillance antepartum *plus* postpartum prophylaxis if positive family history of VTE Consider prophylactic LMWH if multiple additional maternal/pregnancy risk factors for VTE (as below)
Thrombophilia and adverse pregnancy outcomes (APOs), no prior VTE	
• Recurrent pregnancy loss or other APOs with persistent APLAs (lupus inhibitor or mod-high titer anticardiolipin or anti-beta-2-glycoprotein-I antibodies)	Prophylactic LMWH *plus* aspirin 81–162 mg/d
• Recurrent pregnancy loss or other APO and thrombophilia other than APLA	No indication for LMWH to improve pregnancy outcome
***Multiple* (≥3) maternal/pregnancy risk factors for VTE**	
• Women with multiple (≥3) VTE risk factors (Table 1) have a risk for pregnancy-associated VTE of >1%	Prophylactic LMWH, *plus* postpartum prophylaxis

VTE, venous thromboembolism; APLA, antiphospholipid antibody; OCP, oral contraceptive pill; LMWH, low-molecular-weight heparin; AT, antithrombin.

Table 4 Indications for postpartum thromboprophylaxis.

Clinical situation	*Recommended therapy (see Table 5)*
• Prior VTE and/or high-risk thrombophilia • Low-risk thrombophilia and family history of VTE in a 1st-degree relative	Resume prophylactic dose of LMWH ~6 h after delivery, then • continue daily × 6 weeks, *or* • switch to therapeutic LMWH on postpartum day 1 and initiate warfarin (continue × 6 weeks)
• Prior recurrent VTE, on long-term anticoagulation or antithrombin deficiency	Initial prophylactic dose of LMWH ~ 6 h after delivery, *then* • resume therapeutic LMWH on postpartum day 1 *and* • initiate warfarin (continue indefinitely for recurrent VTE, continue × 6 weeks for AT-deficiency without prior VTE)
• All other postpartum women	Perform a VTE risk factor assessment (Table 1): • If 0–1 VTE risk factors, mobilize and hydrate only • If 2 VTE risk factors: ◦ give prophylactic dose of LMWH ~6 h after delivery, *then* ◦ continue daily until hospital discharge (or up to 10 days) • If ≥3 VTE risk factors: ◦ give prophylactic dose of LMWH ~6 h after delivery, then ◦ continue daily × 6 weeks • *or* ◦ switch to therapeutic LMWH on postpartum day #1 and initiate warfarin (continue × 6 weeks)

VTE, venous thromboembolism; LMWH, low-molecular-weight heparin; AT, antithrombin.

Women with any prior venous thromboembolic event: thrombophilia status unknown or negative

Women with a prior 'idiopathic' (unprovoked) VTE event also appeared to be at a substantial risk (~8%) of recurrent VTE in subsequent pregnancy.[16] The VTE recurrence risk is also high among women with prior VTE in whom the original 'secondary' risk factor was estrogen – either a prior pregnancy-related VTE event (antepartum or postpartum) or associated with the use of exogenous estrogen (in combined oral contraceptives, topical estrogens or during hormone replacement therapy). These women have an estimated recurrence risk of ~6.4%[21] (similar to those with a prior idiopathic clot).[22] Another cohort study confirmed an antepartum VTE recurrence risk of 7.5% if the original VTE event was either unprovoked or related to estrogen (pregnancy or oral contraceptive use).[23] These women all merit thromboprophylaxis during their subsequent pregnancies (Table 3) and postpartum (Table 4).

In contrast, those women with a prior secondary risk factor (provoked clot) which has resolved – and who are thrombophilia negative – appear to be at a low risk for recurrent VTE events. In the study by Brill-Edwards *et al.*,[12] there were zero events among 44 such pregnancies. Another cohort study identified that "no recurrence occurred if the first VTE was related to (other) transient risk factors".[23] VTE risk should thus be discussed with these women, with a preference for close clinical surveillance during pregnancy, and a low threshold to investigate any worrisome symptoms of recurrent VTE.

1. Women with a prior 'idiopathic' or unprovoked VTE event should receive active thromboprophylaxis with LMWH

throughout pregnancy and for ~6 weeks postpartum.

2. Women with a prior 'estrogen-related' VTE event should receive active thromboprophylaxis with LMWH throughout pregnancy and for ~6 weeks postpartum.
3. Women with a prior 'secondary' or provoked VTE event (other than estrogen-related) should have close clinical surveillance during pregnancy and be considered for postpartum prophylaxis.

Women with a thrombophilia but without a prior thromboembolic event

Thrombophilias are identified frequently among women who develop venous thromboses during pregnancy,[24] but they are also very common in the general population – with a combined prevalence of up to 15%[11] (Table 2). Physicians may thus encounter young women with genetic or acquired thrombophilia who have never experienced a venous thromboembolic event. This identification of a latent thrombotic tendency is largely due to family screening – and leads to concern regarding their risk of thrombotic events in high risk situations, including during pregnancy/puerperium. Physicians must advise these women about their risk of thromboembolic events and make judicious recommendations about the appropriateness of the preventative use of anticoagulants.

While women harboring a thrombophilia are at above-average risk of developing a VTE during pregnancy,[25,3,5] the magnitude of this risk in an individual varies. There is a heterogeneity of risk among the thrombophilias, with some conferring greater thrombotic risk in pregnancy than others (Table 2).[26,27] Thrombophilic women should therefore undergo an individualized risk assessment based on the type of their thrombophilia, the presence or absence of a family history of VTE, and on the presence other VTE risk factors.[27] The various contemporary international clinical practice guidelines vary somewhat in their recommendations in regard to women with 'asymptomatic' thrombophilias (Table 6).

High-risk thrombophilias (Table 2):

The following thrombophilias are associated with a high primary risk of pregnancy-associated venous thrombosis (>1%):

- homozygous factor V Leiden
- homozygous prothrombin gene 20210A mutations
- antithrombin deficiency
- any combined/multiple low risk thrombophilias.

Given the particularly high VTE risk associated with these thrombophilias, contemporary clinical practice guidelines[28,20,17,13,29] generally recommend active thromboprophylaxis with LMWH – throughout pregnancy and postpartum (Tables 3, 4 and 6).

Women without prior VTE who have a high-risk thrombophilia should receive thromboprophylaxis with LMWH throughout pregnancy and for ~6 weeks postpartum.

Low-risk thrombophilias (Table 2):

Women with all other thrombophilias are considered low risk for primary pregnancy-associated VTE:

- heterozygous factor V Leiden
- heterozygous prothrombin gene mutation
- Protein C deficiency
- Protein S deficiency
- persistent APLAs (without prior VTE).

As the risk of a primary VTE event remains <1% for most of these pregnant women (Table 2), it is not prudent to recommend routine prophylactic anticoagulant therapy. They should be counseled regarding active surveillance for symptoms of VTE during pregnancy – with a low threshold to investigate for DVT or PE if any concerning symptoms

occur. Thromboprophylaxis during pregnancy may still be considered among these lower-risk thrombophilic women if they have multiple additional concurrent VTE risk factors (Tables 1 and 3) or a particularly severe family history of thrombosis.

Postpartum thromboprophylaxis is generally recommended for thrombophilic women who have a positive family history of VTE in a first-degree relative (Tables 4 and 5) – though the various contemporary clinical practice guidelines vary somewhat in their recommendations (Table 6) and some suggest that this may be unnecessary among women with the lowest-risk thrombophilias (heterozygous factor V Leiden or prothrombin gene mutation).

Table 5 Anticoagulants used for thromboprophylaxis during pregnancy and postpartum.

Anticoagulant	Indication for use	Recommended dosage
Low molecular weight heparin (LMWH)	Prevention of VTE in pregnancy and/or postpartum	**Prophylactic LMWH** • *Enoxaparin* 40 mg SC OD (obese: 60 mg OD) • *Dalteparin* 5000 IU SC OD (obese: 7,500 IU OD) • *Tinzaparin* 4500 IU SC OD *or* 75 IU/kg OD **Therapeutic LMWH (for prior recurrent VTE or primary prophylaxis in AT deficiency)** • *Enoxaparin* 1.5 mg/kg SC OD *or* 1 mg/kg BID • *Dalteparin* 200 IU/kg SC OD or 100 IU/kg BID • *Tinzaparin* 175 IU/kg SC OD
Warfarin	Prevention of VTE in postpartum women	• Initial warfarin dose ~5 mg PO OD, adjusted to INR 2.0–3.0 • Overlap with therapeutic LMWH until INR >2.0 for 24 h
Unfractionated heparin (UH)	***LMWHs are strongly preferred*** to UH during pregnancy and postpartum due to their favorable pharmacokinetics and reduced side-effect profile Sodium heparin: 5000 IU (in 0.2 ml) SC BID in 1st trimester, 7500 IU BID in 2nd trimester and 10,000 IU BID in third trimester	
Danaparoid	A synthetic heparinoid which can be used in pregnancy, typically as an alternative to LMWH or UH under the supervision of a hematologist in women intolerant of LMWH (HIT or severe skin reaction). Usual prophylactic dose: 750 IU SC BID	
Fondaparinux	A synthetic analog of the AT-binding pentasaccharide which directly inhibits Factor Xa. Typically used as an alternative to LMWH or UH in pregnancy under the supervision of a hematologist in women intolerant of LMWH (HIT or severe skin reaction). Usual prophylactic dose: 2.5 mg SC OD	
DOACs: dabigatran, rivaroxaban, apixaban	These agents exist as small molecules which cross the placenta and appear in breast milk. They are likely to be active when received orally by a neonate through lactation. They should therefore **NOT be used** during pregnancy or while breastfeeding	

DOACs, direct oral anticoagulants; LMWH, low-molecular-weight heparin; UH, unfractionated heparin; AT, antithrombin; HIT, heparin-induced thrombocytopenia; SC, subcutaneous; OD, once daily; BID, twice daily; INR, internationalized normal ratio; obese: body-mass index (BMI) ≥30 based on pre-pregnancy weight.

Table 6 Recommendations for primary thromboprophylaxis for asymptomatic thrombophilias during pregnancy.

		ASH (USA)[17]		SOGC (Canada)[16]		RCOG (UK)[20]		ACOG (USA)[28]		ANZJOG (ANZ)[29]	
Thrombophilia	**FHx VTE**	**AP**	**PP**	**AP**	**PP**	**AP**	**PP**	**AP**	**PP**	**AP**	**PP**

		ASH (USA)[17]		SOGC (Canada)[16]		RCOG (UK)[20]		ACOG (USA)[28]		ANZJOG (ANZ)[29]	
Thrombophilia	**FHx VTE**	**AP**	**PP**	**AP**	**PP**	**AP**	**PP**	**AP**	**PP**	**AP**	**PP**
FVL heterozygous	N	N	N	N	If add'l RFs	If add'l RFs	If add'l RFs	N	If add'l RFs	N	N
	Y	Y	Y	Y	Y	Consider	Y	Y	Y	Consider	Y
FVL homozygous	N	Y	Y	Y	Y	Consider	Y	Y	Y	If add'l RFs	Y
	Y	N	N	N	If add'l RFs	If add'l RFs	If add'l RFs	Y/N	Y	If add'l RFs	Y
PGM heterozygous	N	N	N	N	If add'l RFs	If add'l RFs	If add'l RFs	N	If add'l RFs	N	N
	Y	Y	Y	Y	Y	Consider	Y	Y	Y	Consider	Y
PGM homozygous	N	N	Y	Y	Y	Consider	Y	Y	Y	If add'l RFs	Y
	Y	Y	Y	Y	Y	Consider	Y	Y	Y	Y	Y
AT deficiency	N	N	N	Y	Y	Consider	Y	Y	Y	If add'l RFs	Y
	Y	N	Y	N	If add'l RFs	Consider	Y	Y/N	Y	Consider	Y
Protein C deficiency	N	N	N	N	If add'l RFs	Consider	Y	N	If add'l RFs	If add'l RFs	Y
	Y	N	Y	N	If add'l RFs	Consider	Y	Y/N	Y	Consider	Y
Protein S deficiency	N	N	N	N	If add'l RFs	Consider	Y	N	If add'l RFs	If add'l RFs	Y
	Y	Y	Y	Y	Y	Consider	Y	Y	Y	Consider	Y
Combined TPs	N	Y	Y	Y	Y	Consider	Y	Y	Y	If add'l RFs	Y

FHx VTE, venous thrombosis in a 1st-degree family member; FVL, factor V Leiden; PGM, prothrombin G20210A gene mutation; AT, antithrombin; TP, thrombophilia; Y, recommend thromboprophylaxis; N, recommend against thromboprophylaxis.

Consider, 'consider' using thromboprophylaxis; If add'l RFs, additional VTE risk factors are present; Y/N, May undertake clinical surveillance for VTE or give thromboprophylaxis.

1. Women without prior VTE who have a low-risk thrombophilia should not receive routine prophylactic anticoagulant therapy during pregnancy – but should all have an individualized VTE risk assessment and be counseled regarding active surveillance for symptoms of VTE during pregnancy.
2. Most women with a low-risk thrombophilia and a positive family history of VTE in a first-degree relative should be considered for thromboprophylaxis for ~6 weeks postpartum.

Women with a thrombophilia and recurrent pregnancy loss and/or other adverse pregnancy outcomes (but no prior VTE)

Women with any of the following persistently detectable antiphospholipid antibodies:

- anticardiolipin antibodies (IgG or IgM in moderate-high titer)
- anti-beta-2-glycoprotein-I antibodies (IgG or IgM in moderate-high titer)
- lupus inhibitor

are at increased risk of adverse pregnancy outcomes – including recurrent spontaneous abortion, unexplained fetal death, placental insufficiency, and early or severe pre-eclampsia.[14] Among women with the obstetrical antiphospholipid antibody syndrome (Table 3), treatment during pregnancy with low-dose aspirin +/− prophylactic-dose LMWH has been demonstrated to improve pregnancy outcome.[14,30,31] The persistent presence of APLAs may also be considered as a risk factor for VTE – of a similar magnitude to other low-moderate risk thrombophilias. Given the increased risk of adverse pregnancy outcomes (including pre-eclampsia) in these women, the use of aspirin (81–162 mg/day) should be considered in all women who harbor APLAs[14] (even if they do not fulfill criteria for APLA syndrome).

Epidemiological data from the past 20 years also identified that women with adverse pregnancy outcomes (including early, severe pre-eclampsia as well as recurrent pregnancy loss, placental abruption, fetal growth restriction, and stillbirth) are more likely to have hereditary thrombophilias than women without these outcomes. This association led clinicians and investigators to pursue research into whether anticoagulants may also be useful to improve subsequent pregnancy outcomes in this population. Such research was difficult and took many years to complete – but ultimately revealed that the use of LMWH during pregnancy did not consistently improve pregnancy outcomes among women with hereditary thrombophilias.[32,33] The American College of Obstetrics and Gynecology concurs that “screening for inherited thrombophilias is not recommended for women with a history of fetal loss or adverse pregnancy outcomes including abruption, pre-eclampsia, or fetal growth restriction”.[27] The VTE risk of any underlying thrombophilia should be considered as part of an individualized VTE risk assessment.

1. Thrombophilia testing of women with unexplained recurrent pregnancy loss or other adverse pregnancy outcomes should be restricted to the measurement of antiphospholipid antibodies.
2. Women with the obstetrical antiphospholipid antibody syndrome (Table 2), should receive low-dose aspirin (81–162 mg/d) +/− prophylactic-dose LMWH throughout pregnancy in order to improve pregnancy outcomes.
3. Women with a hereditary thrombophilia and a history of adverse pregnancy outcomes should not routinely receive thromboprophylaxis in order to improve pregnancy outcomes. They may, however, be considered for thromboprophylaxis as part of an individualized VTE risk assessment .

Women with multiple risk factors for VTE

Antepartum

It is widely recognized that women with multiple clinical risk factors (Table 1) may be at substantial risk of pregnancy-associated VTE.[2,3,4,5] This has variously been defined as ≥2 or 3 concurrent risk factors. A family history of VTE also serves as an independent risk factor for pregnancy-associated VTE,[34,35] even in the absence of a detectable

thrombophilia. In order to recognize and potentially offer thromboprophylaxis to protect these women from VTE, many experts recommend periodic individualized risk assessment for VTE:

- in early pregnancy
  during any hospitalisations
- at the time of delivery.

The latest guidelines from the Royal College of Obstetricians and Gynaecologists (RCOG) in the United Kingdom[20] outline a suggested VTE risk assessment tool. Even in the absence of a prior history of VTE or thrombophilia, women with multiple risk factors appear to have a pregnancy-associated VTE risk of >1% – and therefore should be offered thromboprophylaxis with LMWH during pregnancy (Tables 1 and 3 and available online: https://www.calculosaurus.com/vte-risk-and-dalteparin-checklist).

Women with multiple (≥3) clinical risk factors should be offered thromboprophylaxis with LMWH during pregnancy.

Postpartum

Epidemiological data have shown that the postpartum interval is the period of highest day-to-day risk for serious VTE events; approximately half of all VTE events[6] and up to two-thirds of fatal events[36] occur in this narrow 6 week interval. Women with low-risk thrombophilias should receive thromboprophylaxis after delivery if they have a family history of VTE or any additional concurrent risk factors postpartum (Table 1). Cesarean section (particularly emergency cesarean during labor) has been identified as a particularly potent risk factor, associated with >50% of fatal postpartum pulmonary emboli.[36] The risk of postpartum thromboembolism also markedly increases with the presence of additional VTE risk factors (Table 1).

Guidelines from the RCOG recommend that VTE risk be assessed at the time of delivery, with postpartum thromboprophylaxis administered to women at 'elevated risk' – particularly those with ≥2 VTE risk factors in whom the estimated risk of postpartum VTE exceeds 1% (Table 4 and available online risk calculator: https://www.calculosaurus.com/vte-risk-and-dalteparin-checklist). This individualized postpartum VTE risk-assessment approach avoids the cost and side-effects of 'routine' thromboprophylaxis – restricting the practice to higher-risk women who will benefit most. This judicious practice has been endorsed in other contemporary clinical practice guidelines, and a validated risk prediction model regarding postpartum VTE risk has recently been published.[37] When indicated, postpartum thromboprophylaxis should be continued at least until hospital discharge (or up to 10 days), with extended prophylaxis for up to 6 weeks considered in particularly high-risk women (prior VTE, thrombophilia, ≥3 risk factors) (Table 4).

Women with multiple (≥2) clinical risk factors should be offered temporary postpartum thromboprophylaxis with LMWH (or warfarin), with therapy extended to 6 weeks for women with ≥3 risk factors.

WHAT THROMBOPROPHYLAXIS SHOULD BE USED IN PREGNANCY OR POSTPARTUM?

Antepartum thromboprophylaxis

Prophylactic anticoagulation during pregnancy should ideally be undertaken with low-molecular-weight heparin (LMWH).[28,20,17] Heparin products consist of chains of polysaccharides with alternating residues of D-glucosamine and uronic acid. Low-molecular-weight heparins are produced by the enzymatic cleavage of unfractionated heparin (UH) molecules.[38] The various different LMWH products have chains of slightly different lengths but with similar pharmacokinetic properties. The heparins (UH and LMWH) pose no risk of fetal harm as their large molecules do not cross the placenta.[39] Studies have confirmed equivalent or superior efficacy and safety of LMWH to UH, and maternal side-effects of LMWH therapy (heparin-induced thrombocytopenia [HIT] and osteoporosis) are fortunately rare in pregnancy – and much less common with LMWH than UH. In women with suspected or confirmed HIT (or a history thereof), alternative anticoagulants (danaparoid, fondaparinux) must be considered (Table 5).

Although the physiological changes of pregnancy alter the metabolism of LMWH, resulting in lower peak levels and an enhanced rate of clearance of these medications, evidence suggests that thromboprophylaxis may be undertaken with fixed doses of LMWH throughout pregnancy[40] without a need for therapeutic drug monitoring. For women already on indefinite therapeutic anticoagulation (i.e. prior recurrent thromboses) as well as women who are 'heparin-resistant' due to antithrombin deficiency, therapeutic LMWH should be maintained throughout pregnancy. The addition of aspirin (81–162 mg/day) is generally restricted to women with antiphospholipid antibodies, particularly those with prior recurrent adverse pregnancy outcomes. Women at increased risk for recurrent VTE may also be encouraged to wear elastic compression stockings to prevent venous distension and further reduce their thrombotic risk.[20] Intermittent pneumatic compression of the lower extremities may be considered when hospitalized for any reason and placed on bedrest – or particularly if interruption of pharmacologic prophylaxis is required (during the peripartum interval or in the setting of bleeding)[28,17] – with a plan for resumption of both mobilization and pharmacologic thromboprophylaxis as soon as possible.

The use of warfarin (or other coumarins) for ongoing anticoagulation during pregnancy is largely restricted to women with mechanical heart valves, in whom the risk of maternal thromboembolic complications is particularly high.[41] The use of a warfarin during pregnancy poses a significant risk of fetal harm (due to teratogenesis and fetal bleeding complications) and fetal loss[42] – but may be considered for VTE prevention in clinical settings or countries in which LMWH is unavailable.

Peripartum thromboprophylaxis

LMWH therapy must be interrupted temporarily during labor and the immediate peripartum interval to minimize the risk of hemorrhage and to (ideally) facilitate the option of regional anesthesia. Due to the theoretical risk of paraspinal hemorrhage in women receiving heparin who undergo epidural or spinal anesthesia, many anesthetists are unwilling to perform neuraxial regional anesthetic on women who have received LMWH within the preceding 12 hours (prophylactic dosing) to 24 hours (with therapeutic dosing). There are very limited data about the actual risk of this rare complication in pregnant women, but this cautious approach is supported by recent practice guidelines from the American Society of Regional Anesthesia and the Society for Obstetric Anesthesia and Perinatology.[43,44]

To facilitate the option of regional anesthesia for these women, options include:

1. Elective discontinuation of LMWH 12–24 hours prior to a planned induction of labor or a scheduled cesarean section (if indicated for obstetric reasons);
2. Prompt discontinuation of LMWH in the earliest stages of spontaneous labor[20] – hoping that at least 12 hours has passed since the last LMWH dose at the time regional anesthesia is desired/needed;
3. Elective discontinuation of prophylactic dose LMWH at ~38 weeks' gestation, to await spontaneous labor (accepting a small risk of VTE in the remaining weeks of pregnancy). Unfractionated heparin may be substituted at an equivalent dose until onset of labor, if desired.

Selection among these choices may vary by center and according to patient values/preferences. In the setting of excessive/ongoing peripartum hemorrhage, in which the recent administration of LMWH (either prophylactic or therapeutic) is felt to be contributing, protamine sulfate or recombinant factor VIIa can be administered to partially reverse the remaining anticoagulant effect.[45,46]

Postpartum thromboprophylaxis

Ongoing thromboprophylaxis of high-risk women is essential in the postpartum period. Postpartum VTE events are clustered within the first 2–6 weeks postpartum[9] making this the highest risk period for pregnancy-associated VTE events, and thus an ideal period for targeted thromboprophylaxis of women at increased risk. Intermittent pneumatic compression of the lower extremities (or the use of graded compression stockings) should be considered during the immediate peripartum interval among women at high VTE risk, and pharmacologic thromboprophylaxis should be promptly resumed once obstetric hemostasis is confirmed – ideally within 6 hours of delivery.[20]

In most women, prophylactic-intensity LMWH (Table 5) may be given subcutaneously, with an initial dose starting 4–

6 hours after delivery. Ongoing postpartum thromboprophylaxis may subsequently be undertaken with either continued prophylactic LMWH or a transition to warfarin. LMWHs do not enter breast milk in significant concentrations and, since they are also not orally absorbed in the neonate, can be used safely during lactation.[17] Although warfarin may appear in minute amounts in breast milk, it has not been associated with adverse newborn events in healthy, full-term infants and is considered compatible with breastfeeding by the American Academy of Pediatrics.[47] The majority of women undertaking short-term (≤6 weeks) postpartum thromboprophylaxis will prefer the simplicity of a daily injection of LMWH to the complexity of oral anticoagulation with warfarin.

If warfarin is selected (including patients requiring ongoing/indefinite therapeutic anticoagulation), therapeutic-intensity LMWH and warfarin may be commenced on the first postpartum day (following an initial prophylactic dose of LMWH ~6 hours postpartum) and overlapped until the INR is therapeutic for over 24 hours. This higher-intensity LMWH therapy is required because these women typically have pregnancy-associated protein S deficiency – and therefore an increased risk for warfarin-associated hypercoagulability (skin necrosis, etc.) during the initiation of warfarin. With the advent of pharmacist-directed outpatient anticoagulation monitoring services, which are associated with improved efficacy and reduced bleeding,[48] this does not typically delay hospital discharge. Some physicians prefer to delay the initiation of warfarin for several days to weeks, however, utilizing LMWH alone in the immediate postpartum period to allow wound healing and potentially reduce the risk of postpartum hemorrhage and wound hematomas (following cesarean section).

The newer direct oral anticoagulants (dabigatran, rivaroxaban, apixaban) exist as small molecules which appear in breast milk – and are likely to be active when received orally by a neonate through lactation.[20] They should therefore not be used during breastfeeding.

Prophylactic anticoagulation should be continued at least until hospital discharge (the RCOG recommends 10 days postpartum),[20] and for a minimum of 6 weeks postpartum in high-risk women (prior VTE, thrombophilias, ≥3 clinical VTE risk factors) – at which point the physiological changes in the coagulation system related to pregnancy will have largely returned to normal and the thrombotic risk diminished.[9]

SUMMARY

VTE remains a serious cause of maternal morbidity and mortality in pregnancy and postpartum. Given the increasing age, obesity and medical complexity of the maternal population, thromboprophylaxis in pregnancy will remain an important issue for the foreseeable future. Physicians caring for these women will require expertise in the management of these patients, including judicious selection and dosing of appropriate prophylactic anticoagulant medications during pregnancy as well as skill in the management of anticoagulation during the peri- and postpartum intervals.

PRACTICE RECOMMENDATIONS

Women who merit prophylactic anticoagulation with LMWH *during pregnancy* to prevent VTE:

Prior VTE:

- **unprovoked**
- **associated with a thrombophilia**
- **estrogen-associated**
- **recurrent (continue therapeutic anticoagulation with LMWH if anticoagulated prior to pregnancy).**

No prior VTE:

- **high-risk thrombophilia (homozygous factor V Leiden, homozygous prothrombin 20210A gene mutation, antithrombin deficiency, combined thrombophilias)**
- **Women with *multiple* (3 or more) risk factors for VTE (Table 1).**

Women who merit prophylactic anticoagulation *postpartum* to prevent VTE:

- **Women on LMWH during pregnancy for any indication**
  - ***6 weeks***
- **Prepregnancy anticoagulation**
  - ***resume indefinite therapeutic anticoagulation with oral anticoagulant (warfarin)***
  - ***Avoid direct oral anticoagulants (DOACs) during lactation***
- **Low-risk thrombophilia (heterozygous factor V Leiden, heterozygous prothrombin 20210A gene mutation, protein C or S deficiency, persistent APLA positivity [no prior VTE]) *PLUS* a family history of VTE in a first-degree relative:**
  - ***6 weeks***
- **Women with a moderate-high risk of postpartum VTE based on an individualized risk assessment (2 or more VTE risk factors (RFs))**
  - ***until hospital discharge or up to 10 days for women at moderate risk (2 RFs)***
  - ***6 weeks in women at high risk (3 or more RFs)***

Recommended anticoagulants (Table 4):

- **For thromboprophylaxis during pregnancy: low-molecular-weight heparin (LMWH)**
- **For thromboprophylaxis postpartum: LMWH or warfarin.**

CONFLICTS OF INTEREST

Author statement awaited.

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