Preventing venous thromboembolism during pregnancy and postpartum: crossing the threshold

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When should a patient with a known thrombophilia or prior venous thromboembolism (VTE) receive low-molecular-weight heparin (LMWH) prophylaxis during pregnancy and/or the postpartum period? Accurately predicting thrombotic and bleeding risks and knowing what to do with this information is at the heart of decision-making in these challenging scenarios. This article will explore the concept of a risk threshold from clinician and patient perspectives and provide guidance for the use of antepartum and postpartum LMWH prophylaxis in women with a known thrombophilia or prior VTE. Advice for the management of LMWH prophylaxis use around labor and delivery is also reviewed.

Learning Objectives

- Describe the risk of venous thromboembolism (VTE) among pregnant women with inherited thrombophilia, antiphospholipid syndrome, and those with prior VTE
- Apply the concept of a VTE risk threshold to make decisions about anticoagulation prophylaxis in pregnancy and the postpartum period

Introduction

When should a patient with a known thrombophilia and/or prior venous thromboembolism (VTE; the term includes both deep vein thrombosis [DVT] and pulmonary embolism) receive low-molecular-weight heparin (LMWH) prophylaxis during pregnancy and/or the postpartum period? Asking the following 2 questions can help us to approach this problem: (1) At what threshold of VTE risk should thromboprophylaxis be considered in the antepartum or postpartum period? and (2) What is the risk of VTE during pregnancy or the postpartum period for a particular patient? Accurately predicting thrombotic and bleeding risk and knowing what to do with this information is at the heart of decision-making in these challenging scenarios.

At what threshold of VTE risk should thromboprophylaxis be considered in the antepartum or postpartum period?

The clinicians' perspective: a calculated approach

Randomized trials that evaluate thromboprophylaxis in pregnancy or the postpartum period have been challenging to conduct.[1] Instead, recommendations are based on estimating baseline VTE risk and the presumed risk and benefit of thromboprophylaxis. LMWH is the anticoagulant of choice in pregnancy because of its superior safety profile; unfractionated heparin has a higher risk of heparin-induced thrombocytopenia and osteoporosis with prolonged use, and warfarin and the direct oral anticoagulants (DOACs) carry a potential risk of congenital malformations.[2] Using LMWH prophylaxis is warranted when the benefits of treatment outweigh the risks or when LMWH prevents more important thrombotic events more often than it causes important bleeding. Although this balance seems obvious, it raises the following question: What is an important outcome? One major challenge when setting a threshold is that not all VTE and bleeding events have equivalent outcomes. The proportion of fatal VTE or bleeding events, also known as VTE or bleeding case fatality rates, should also be considered.[3]

VTE and bleeding case fatality rates have been reported in the nonpregnant population, but less data are available for those who are pregnant. In a meta-analysis of orthopedic surgery patients who received prophylactic anticoagulation, the proportion of fatal bleeds was 2 to 3 times higher than the proportion of fatal VTEs (3.6% [95% confidence interval (CI), 3.2%-3.9%] vs 1.4% [95% CI, 0.9%-2.2%]).[4] Similarly, fatal bleeding occurred 3 times more often than fatal VTE among patients who were not pregnant and who received anticoagulation therapy for VTE.[5] In studies of pregnant women, the proportion of fatal VTE ranges from 0% to 1.91%, with a pooled VTE case fatality rate of 0.68% (95% CI, 0.41%-0.96%)[6]; however, not enough data are available to estimate the risk of fatal bleeding with LMWH prophylaxis in pregnancy. Hemorrhage, an important cause of maternal mortality, was attributed to 11.4% of pregnancy-related deaths in the United States between 2011 and 2013, and important antepartum bleeding may affect fetal viability. Therefore, based predominantly on data from the nonpregnant population, if we assume that fatal bleeding with LMWH prophylaxis is 2 to 3 times more likely than fatal VTE in pregnancy, LMWH prophylaxis would have to prevent 2 to 3 more VTE events to provide benefit for every major bleed reported.

Bleeding risk can be overlooked. Clinicians and patients often overestimate benefit and underestimate harms of interventions.[7] In a meta-analysis that combined patient level data from 8 randomized trials to evaluate LMWH prophylaxis for prevention of placenta-mediated

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Off-label drug use: LMWH to prevent VTE in pregnancy.

pregnancy complications, the risk of antepartum major bleeding was 0.2% (1 of 470), and the risk for postpartum major bleeding was 0.6% (3 of 473) with LMWH prophylaxis.[8] In a meta-analysis that evaluated LMWH safety in 64 studies and 2777 pregnancies, the severe antepartum bleeding risk was 0.43% (95% CI, 0.22%-0.75%) and postpartum bleeding risk (>500 mL) was 0.94% (95% CI, 0.61%-1.37%),[9] with the risk of bleeding similar to risks reported with prophylactic doses alone (0.42% and 0.92%, respectively). Unfortunately, the majority of these studies do not divide out early (<24-hour) vs late (≥24-hour) postpartum bleeding, and some studies used LMWH <24 hours from delivery, which limits our ability to estimate bleeding risk that is attributed to LMWH prophylaxis. Instead of setting a VTE risk threshold that matches bleeding risk (antepartum >0.75% or postpartum >1.37%, using the upper bound of the 95% CIs to be conservative), setting a VTE risk threshold that is 2 to 3 times higher at ~3% may help counteract the additional risk associated with major bleeding in pregnancy or the postpartum period.

Differences in a VTE risk threshold will lead to different recommendations for LMWH prophylaxis during pregnancy. For example, the Society of Obstetricians and Gynecologists of Canada and the American College of Chest Physicians provide different recommendations for postpartum LMWH prophylaxis based on different VTE thresholds for postpartum LMWH prophylaxis (>1% and >3%, respectively).[2,10] On the basis of an anonymous vote of international thrombosis pregnancy experts, the majority (60%) chose 3% or greater as a VTE risk threshold for antepartum prophylaxis and 3% or greater as a VTE risk threshold for postpartum prophylaxis; however, not all experts agreed.[11] Acknowledging that risk thresholds differ between guidelines, clinicians, and patients is an important aspect of managing pregnant patients at risk of VTE.

The patients' perspective: a holistic approach

When making decisions about LMWH prophylaxis, patients may place different values on preventing thrombosis or bleeding,[12] or they may consider additional factors such as daily injections (up to 400 injections per pregnancy), significant cost (>US$4000 per pregnancy), medicalization of a pregnancy, and other possible adverse effects.[2]

An international interview-based study of 123 women with past VTE who were currently pregnant or planning a pregnancy showed that patients' decisions to use LMWH were difficult to predict. The majority (86.4%) of participants categorized as having a high risk of VTE recurrence, but importantly not all of them (13.6%), were willing to use LMWH prophylaxis during their pregnancy. Conversely, among low-risk participants for whom LMWH is often not recommended, the majority (60.0%) were willing to use LMWH throughout their pregnancy.[13] Women were also presented with hypothetical scenarios of various VTE risk thresholds; 65% and 90% of participants were willing to use antepartum LMWH prophylaxis when they had an antepartum VTE risk of 4% and 16%, respectively. The only predictive risk factor for willingness to use antepartum LMWH prophylaxis was a history of using LMWH for at least 2 weeks in their previous pregnancies.[13]

If this same group of women was questioned about our calculated VTE risk threshold of 3%, only 60% to 65% would likely agree (based on 2.5% and 4% risk thresholds, respectively, presented to participants), further highlighting the importance of individualized decision making. The best way to communicate VTE risk to patients and help them make decisions is largely unknown and deserves further study.[12]

Table 1. Population-attributable risk of inherited thrombophilia for VTE in pregnancy and the postpartum period

Inherited thrombophilia	Proportion of attributable risk (%)
All inherited thrombophilia	48.3
FVL	
Heterozygous	26.7
Homozygous	7.7
PGM	
Heterozygous	10.4
Homozygous	—*
Compound FVL/PGM	—*
PC deficiency	1.9
PS deficiency	1.5
AT deficiency	0.07
No inherited thrombophilia	51.7

Population-attributable risk is calculated on the basis of relative risk of VTE in pregnancy[16] and prevalence of thrombophilia in the general population.[69]
*Unknown estimates.

Summary of VTE risk threshold: a balanced approach

In summary, there is likely no net clinical benefit to LMWH prophylaxis when the absolute VTE risk in the antepartum or postpartum period is <1%, and there is most likely a net clinical benefit when the absolute VTE risk is >3%. Although I favor use of LMWH when the VTE risk is >3%, I use these numbers as a starting place for my discussions with patients. Even with knowledge of a higher bleeding risk in the postpartum period, patients are more likely to accept a short course of LMWH and a lower VTE risk threshold in the 6-week postpartum period in which the per-day risk of VTE is highest compared with the ~40-week commitment to LMWH injections.

What is the risk of VTE for pregnant patients with inherited thrombophilia, antiphospholipid syndrome, or prior VTE and what are the recommendations for LMWH prophylaxis?

Inherited thrombophilia

Inherited thrombophilias, a group of hereditary hypercoagulable blood disorders that predispose to thrombosis,[14] increases the risk of VTE in pregnancy to varying degrees. The incidence of VTE in the general pregnant population is approximately 1.2 to 1.4 per 1000 deliveries.[6,15] Among the general pregnant population, inherited thrombophilia accounts for almost half (48%) of the VTE risk seen in the pregnant and postpartum period (Table 1).

Family history is important. There is variation in the risk of VTE reported for each of the inherited thrombophilias, partly because of the presence or absence of a family history of VTE and study design. Studies that investigate relatives of family members with known VTE and thrombophilia report higher risks of VTE in pregnancy, whereas studies that are not family based[16] and randomized controlled trials that include patients with inherited thrombophilia[3] typically report a lower risk of VTE. A family history of VTE increases an individual's VTE risk as much as 2 to 4 times,[17,18] regardless of thrombophilia status. The family members included in the studies vary from first-degree relatives only[19-22] to any relative,[22-25] with little information available on the VTE event type for family members.[19]

Before reviewing risk estimates and recommendations for inherited thrombophilia, it is important to address a few points. Most studies

Table 2. Absolute VTE risk in pregnancy and postpartum in asymptomatic women with inherited thrombophilia with and without a family history

Inherited thrombophilia	Family history of VTE*	Combined antepartum and postpartum risk (%)	95% CI
FVL			
Heterozygous	No	1.2	0.8-1.8
Heterozygous	Yes	3.1	2.1-4.6
Homozygous	No	4.8	1.4-16.8
Homozygous	Yes	14.0	6.3-25.8
PGM			
Heterozygous	No	1.0	0.3-2.6
Heterozygous	Yes	2.6	0.9-5.6
Homozygous	No	3.7	0.2-78.3
Homozygous	Yes	—	
Compound FVL/PGM†		5.5	0-21.92
PC deficiency			
	No	0.7	0.3-1.5
	Yes	1.7	0.4-8.9
		0	0-25.9 (total)
		0	0-79.4 (no prophylaxis)
PS deficiency			
	No	0.5	0.2-1.0
	Yes	6.6	2.2-14.7
		0	0-32.4 (total)
		0	0-48.9 (no prophylaxis)
AT deficiency			
	No	0.7	0.2-2.4
	Yes	3.0	0.08-15.8
		8.3	1.4-35.4 (total)
		14.3	2.6-51.3 (no prophylaxis)

Table adapted from Bates et al[11] with calculated risk based on a baseline VTE incidence of 1.4 per 1000 pregnancies from a non–family-based population study.[70] The antepartum and postpartum risks are roughly equal (half the total events occurring antepartum and half postpartum).[6,20,26,27] Certain thrombophilias such as heterozygous FVL, heterozygous PGM, and PS deficiency have a higher VTE risk reported in the postpartum period.[19,23,25,28,71]

*The definition of family history varies according to each study.

†Based on data from Gerhardt et al,[17] which includes a population with and without family history of VTE.

report VTE risk by combining the antepartum and postpartum period, but in reality, we make decisions by considering the antepartum and postpartum periods separately (Table 2). Although these risk estimates are static, true risk assessment should be dynamic and should take place over multiple time points. Although a single transient risk factor such as immobilization may be associated with a small increase in VTE risk, when it is combined with thrombophilia, prophylaxis may be warranted.

Heterozygous factor V Leiden or prothrombin gene mutation. Women who are heterozygous for factor V Leiden (FVL) or prothrombin gene mutation (PGM) with no personal or family history of VTE have a very low risk of VTE in the antepartum (<1%) or postpartum period (<1%)[17,26,27] (Table 2).

Among women who are heterozygous for FVL or PGM and who have a family history of VTE, the absolute VTE risk in the antepartum or postpartum period is somewhere between 1% and 3%[11] (Table 2). Among the FVL and PGM family-based studies, the majority of pregnancy-related VTE events took place in the postpartum period.[19,28] A more recent case-control study by Gerhardt et al[17] found no interaction between family history and VTE risk for heterozygous women with FVL, with reassuringly low risks of VTE (0.5% [95% CI, 0.23%-0.72%) reported across the combined pregnancy and postpartum periods.

Recommendations: In women with no personal or family history of VTE who are heterozygous for FVL or PGM, I do not recommend routine antepartum or postpartum LMWH prophylaxis because of the low (<1%) VTE risk. However, I do review the symptoms of DVT and pulmonary embolism and provide guidance on when to seek medical attention, along with future reassessment of risk (clinical vigilance). I may favor a short course of LMWH for 2 to 3 weeks postpartum for individuals with no family history of VTE who have additional clinical risk factors[11] or for patients with a strong preference, albeit with uncertain benefit. If there is a family history of VTE, then I recommend 6 weeks of LMWH postpartum only, acknowledging that the VTE risk without LMWH in the postpartum period is likely between only 1% and 3% for these women and may be equivalent to the risk of important bleeding.

Protein C and protein S deficiency. Women with protein C (PC) or protein S (PS) deficiency and no family history of VTE also have a low estimated risk (<1%) in the antepartum or postpartum period[16,17] (Table 2). Women with more reduced activity levels of PC (<50%) or PS (<40%) may have an increased risk of VTE; however, this is based on a small sample size and overlapping CIs.[17] Older family-based studies report a slightly higher antepartum or postpartum risk in the 1% to 3% range.[23]

PS levels gradually decrease over the course of pregnancy, so any diagnosis of PS deficiency should be avoided in pregnancy or the immediate postpartum period. Any low levels should be confirmed outside of pregnancy and possibly only acted on if they are well below the reference ranges reported in pregnancy by trimester.[29,30]

Recommendations: Among women with PC or PS deficiency with no family history of VTE, I recommend clinical vigilance with no

antepartum or postpartum LMWH prophylaxis. As with women who are heterozygous for FVL or PGM, I may consider the addition of postpartum LMWH prophylaxis when additional transient risk factors are present or when there is strong personal preference. Given the recent reassuring VTE risk estimates,[17] I do not recommend routine antepartum prophylaxis for pregnant women with PC or PS deficiency and a family history of VTE unless there are additional risk factors present, but I still recommend 6 weeks of postpartum prophylaxis.

Homozygous or compound heterozygous FVL and PGM. Patients who are homozygous for FVL or PGM are at higher risk of VTE during pregnancy, particularly those with a family history of VTE (antepartum or postpartum risk ~7%-8%)[11] (Table 2). Estimating VTE risk among patients who are homozygous for FVL or PGM poses a unique challenge, because the absence of a family history of VTE is possible if family members carry only 1 copy of the FVL or PGM gene mutation. Therefore, lack of a family history of VTE may be less useful for risk stratification in these patients. Only a few patients have been reported with homozygous FVL or PGM and without a family history of VTE, which contributes to the challenges in estimating VTE risk.[16] For pregnant women who are compound heterozygous for FVL/PGM, there are mixed reports of an intermediate[27,31] or high[17] risk of pregnancy-associated VTE.

Recommendations: In women who are homozygous or compound heterozygous for FVL and PGM and have no family history of VTE, I recommend at least 6 weeks of postpartum LMWH prophylaxis. Given the uncertainty in risk estimates, I do have the discussion about antepartum LMWH prophylaxis on the basis of patient values and preferences; estimating their antepartum VTE risk is uncertain but is likely somewhere in the 1% to 3% range. In women who are homozygous or compound heterozygous for FVL and PGM with a family history of VTE, I recommend both antepartum and postpartum LMWH prophylaxis with risk estimates >3%.

Antithrombin deficiency. The risk among pregnant women with antithrombin (AT) deficiency is difficult to predict and is affected by family history and severity of deficiency (Table 2). Among family cohort studies, the reported VTE risk is 3.0% to 8.3% in the combined antepartum and postpartum period.[22,23] LMWH is dependent on AT activity for its anticoagulant effect, so low levels of AT have the potential to reduce the effectiveness of LMWH prophylaxis in pregnancy.[32]

Recommendations: Among women with AT deficiency and no family history, I suggest 6 weeks of postpartum LMWH prophylaxis, but I focus on patient values and preferences given the lack of data in this area. Among women with AT deficiency and a family history of VTE, I recommend both antepartum and postpartum LMWH prophylaxis, because risk estimates are uncertain but are likely >3%. On the basis of the possibility of relative heparin resistance in moderate to severe AT deficiency, I use intermediate or therapeutic doses of LMWH.[33]

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is diagnosed if at least 1 laboratory criterion and 1 clinical criterion are present. According to the laboratory criteria, patients should have at least 1 of the following: a positive lupus anticoagulant (LAC), anticardiolipin (aCL) antibodies of immunoglobulin G (IgG) and/or IgM isotype >99th percentile or >40 GPL/MPL, or anti-β2 glycoprotein 1 (anti-β2GP1) antibodies of IgG and/or IgM isotype >99th percentile on 2 or more occasions at least 12 weeks apart. According to the clinical criteria, patients should have at least 1 episode of VTE, arterial thromboembolism, small-vessel thrombosis, or placenta-mediated pregnancy complications, based on either 3 consecutive pregnancy losses at <10 weeks gestation, 1 late (≥10 weeks gestation) loss, or preterm delivery <34 weeks because of severe pre-eclampsia, eclampsia, or placental insufficiency.[34]

Patients who received anticoagulation for past VTE or arterial thromboembolism are switched to LMWH when they become pregnant, often at an intermediate or therapeutic dose of LMWH, to prevent recurrent thrombosis during pregnancy. However, how to treat women with only obstetrical manifestations of APS is largely unknown, with little data available to guide practice for VTE prevention. The use of antepartum aspirin and LMWH prophylaxis to prevent pregnancy loss or placenta-mediated pregnancy complications is controversial, based on mixed trial data with small sample sizes and methodologic limitations, and is beyond the scope of this article.[2,35] The remaining discussion will focus on recommendations for VTE prevention only, which may be different than recommendations for prevention of recurrent pregnancy loss.[2,10]

In a pooled analysis of all randomized controlled trials of women with positive LAC or aCL and obstetrical complications, there were no episodes of antepartum VTE reported in the aspirin or placebo study arms (0% [95% CI, 0%-1.2%]) (Table 3). None of the trials reported on postpartum VTE events or included patients with positive anti-β2GP1 antibodies. The majority of trials excluded patients with past systemic lupus erthematosus[36-40] or past VTE.[37-42] In the Thrombophilia in Pregnancy Prophylaxis Study (TIPPS), 1 patient with APS of 22 (4.5%) developed an antepartum VTE. That patient had a prior history of provoked DVT and was receiving antepartum prophylaxis.[43]

The only data available to predict VTE risk in the postpartum period for women with obstetrical APS is extrapolated from antepartum risk estimates (Table 3) and retrospective data. In a retrospective cohort study of 87 patients with positive LAC and/or aCL IgG antibodies and recurrent pregnancy loss, only 4 patients received LMWH prophylaxis postpartum.[44] The reported postpartum VTE risk was 1.1% (95% CI, 0.2%-6.2%): 1 patient with high titer (>51 GPL) aCL and positive LAC developed a DVT postpartum while receiving LMWH prophylaxis.[44] Lupus anticoagulant and higher titer aCL antibodies (>33-40 GPL) are associated with a first episode of thrombosis in the nonpregnant population.[45] In a case-control study of pregnancy-associated VTE, there was no difference in the prevalence of positive antibodies between those with or without pregnancy-associated VTE, but there was a nonsignificant trend favoring multiple antibody positivity among women with VTE.[46]

Recommendations. Among women with APS and prior obstetrical complications, I would not routinely prescribe antepartum LMWH for VTE prevention during pregnancy unless additional risk factors were present or there was a prior history of VTE. I suggest postpartum LMWH prophylaxis among patients with LAC, higher-titer aCL IgG or IgM antibodies, multiple positive antibodies/LAC, or if additional risk factors such as systemic lupus erthematosus (odds ratio 8.7)[11] is present, with a focus on individualized management, given the limited data available. In the absence of data on the risk of thrombosis in obstetrical APS for women with positive anti-β2GP1 antibodies, I make an individualized decision based on the presence of LAC or aCL antibodies and on whether additional risk factors are present.

Prior VTE

Women with a past unprovoked or estrogen-associated VTE are at increased risk of thrombosis during pregnancy (Table 4). For

Table 3. Pooled proportion of VTE among women who did not receive antepartum prophylaxis, in randomized trials of pregnant patients with positive antiphospholipid antibodies and obstetrical complications

		Antepartum risk (aspirin or placebo)	
Reference	**VTE**	**%**	**95% CI**
Prior pregnancy loss			
Silver et al[72]	0/22*		
Kutteh et al[36]	0/25		
Laskin et al[73]	0/46		
Rai et al[37]	0/45		
Pattison et al[38]	0/40		
Farquharson et al[39]	0/47		
Goel et al[74]	0/39		
Laskin et al[42]	0/20		
Subtotal	0/284	0	0-1.3
Prior placenta-mediated pregnancy complications			
Rodger et al[43]	0/10†		
van Hoorn et al[40]	0/16		
Subtotal	0/26	0	0-27.8
Total	0/310	0	0-1.2

Placenta-mediated pregnancy complications include pre-eclampsia, placental abruption, small-for-gestational-age neonate, and late pregnancy loss. The postpartum VTE risk was not reported in any of the included studies.
*Included 1 patient with a prior history of VTE.
†One patient with APS and prior provoked VTE had an antepartum VTE at 11 weeks of gestation while receiving LMWH prophylaxis (LMWH data not shown).

pregnant women with a prior provoked VTE resulting from a major risk factor such as trauma, surgery, or prolonged immobilization, the risk of antepartum VTE recurrence seems lower (1%).[33] Data are limited regarding whether thrombophilia increases the risk of provoked VTE.[47-49] Even less data are available regarding the risk of VTE for patients with a past history of superficial or distal DVT, with a possible increased risk of VTE seen in the postpartum period in the TIPPS trial.[43] Only limited data are available for the risk of recurrent VTE among women with a past history of unusual-site thrombosis. Among 59 women with a prior history of cerebral vein thrombosis (the majority of which were estrogen associated), antepartum and postpartum prophylaxis were effective at preventing recurrent VTE.[50].

Recommendations. I recommend antepartum and postpartum LMWH prophylaxis for all women with a past unprovoked or estrogen-associated VTE. For women with a provoked VTE resulting from a major provoking risk factor, I recommend only postpartum LMWH prophylaxis. For women with a provoked VTE and a thrombophilia, I make an individualized decision based on the type of provoked event, thrombophilia, and patient values and preferences.

Practical considerations for using LMWH prophylaxis

Recommended LMWH dosing strategies vary,[51] and a clinical trial is underway that is evaluating prophylactic vs intermediate doses of LMWH (NCT01828697; Comparison of Low and Intermediate Dose Low-Molecular-Weight Heparin to Prevent Recurrent Venous Thromboembolism in Pregnancy [Highlow]). I use the dosing regimen from the TIPPS clinical trial for patients who are not already receiving anticoagulation: a prophylactic dose of LMWH once per day until 20 weeks gestation (eg, dalteparin 5000 IU once per day, enoxaparin 40 mg, and tinzaparin 4500 IU once per day), with an increase to a twice-per-day regimen after 20 weeks gestation until delivery as a result of changes in the volume of distribution and increased renal clearance in pregnancy, leading to earlier trough levels of anti–Factor Xa activity.[52,53] Because there is no change in bone mineral density with this regimen, I do not routinely prescribe calcium or vitamin D.[54]

In patients who are already receiving anticoagulants or who have potent thrombophilias, such as those with moderate to severe AT deficiency or APS with past thrombosis, I use a 75% or therapeutic dose of LMWH throughout pregnancy. Patients already receiving warfarin before pregnancy are transitioned to LMWH before 6 weeks gestation (ie, with a first positive pregnancy test) to avoid warfarin embryopathy. Warfarin embryopathy typically occurs between 6 and 12 weeks gestation with nasal hypoplasia and stippled epiphyses; limb hypoplasia is also present in a proportion of cases.[2] Because of the lack of teratogenicity data for patients receiving DOACs,[55] I prefer to temporarily switch patients to warfarin or transition to LMWH before conception[56] instead of continuing to receive a DOAC until pregnancy is confirmed.[57] As more data become available about the type and timing of potential DOAC teratogenicity, this recommendation may change.

Given the additional challenge that LMWH prophylaxis adds to labor and delivery, a written plan shared by a multidisciplinary team is needed. I discuss 3 possible options with patients who are receiving prophylactic doses of LMWH to arrive at a decision that is individualized and largely driven by patient preference. The options are to (1) stop LMWH when labor begins, with the possibility that a patient may not be able to receive epidural analgesia; (2) stop LMWH early (ie, at 37 weeks gestation) with exposure to a small risk of VTE during this time; or (3) plan to induce labor and stop the LMWH 12 to 24 hours after the last dose, based on local anesthesiology practice guidelines. An alternative strategy in some centers is to switch from LMWH to unfractionated heparin at term (37 weeks gestation), which is based on insufficient evidence and expert opinion.[10] Patient characteristics, such

Table 4. Absolute VTE risk in pregnancy and postpartum in women with prior unprovoked VTE, estrogen-associated VTE, and provoked VTE

	Antepartum risk*		Postpartum risk†	
Past VTE	**%**	**95% CI**	**%**	**95% CI**
Unprovoked VTE	3.6	1.4-8.9	3.1	0.5-15.7
Estrogen-associated VTE	6.4	3.9-10.4	11.7	5.8-22.2
Provoked VTE (non-estrogen associated)	1.0	0.19-5.7	7.1	1.9-22.6

VTE includes deep vein thrombosis and pulmonary embolism.
*Antepartum risk estimates are derived from pooled proportions among women with no antepartum prophylaxis use.[3]
†Postpartum risk estimates are limited to 1 study without postpartum prophylaxis use (n = 120).[48]

as previous deliveries (multiparous) or short duration of previous labor, may affect a patient's chance of receiving an epidural. With respect to stopping LMWH prophylaxis early, study results are mixed regarding whether the VTE risk is equal throughout pregnancy (ie, antepartum risk divided by 280 days for a per-day risk),[48,49,58] or whether risk increases in the third trimester.[6,59] In my experience, patients are often committed to preventing VTE after completing several months of injections and are reluctant to stop early for this small risk of VTE. Finally, a planned induction allows for using epidural analgesia while minimizing the risks of VTE and bleeding. Although earlier studies reported an increased risk of cesarean delivery with induction of labor, the results were likely confounded by the indication for induction and the methodologic flaw of comparing induction of labor to spontaneous labor rather than expectant management.[60-65] Randomized trials are ongoing to clarify the risk of cesarean delivery with induction of labor. For women receiving a once-per-day 75% or therapeutic dose of LMWH, I favor a planned induction to minimize the risk of bleeding and allow for possible use of an epidural. Postpartum, LMWH is resumed 12 to 24 hours after delivery on the basis of patient risk factors. If patients were previously receiving 75% or full doses of LMWH, I typically start with prophylactic doses and escalate to a higher twice daily dose in hospital to minimize bleeding postpartum. When there is a contraindication to anticoagulation in the postpartum period, I use mechanical prophylaxis and favor intermittent pneumatic compression over elastic compression stockings if available.[2,66] Warfarin and LMWH are safe while breastfeeding[2]; any DOACs should be avoided in breastfeeding.[67,68]

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