Prevention and management of venous thromboembolism in pregnancy: cutting through the practice variation

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There is clinical practice variation in the area of prevention and management of venous thromboembolism (VTE) in pregnancy. There are limited data and differing recommendations across major clinical practice guidelines, especially relating to the role of postpartum low-molecular-weight heparin (LMWH) for patients with mild inherited thrombophilia and those with pregnancy-related VTE risk factors. This chapter explores the issues of practice variation and related data for postpartum VTE prevention. Controversial topics of VTE management in pregnancy are also reviewed and include LMWH dosing and the role of anti-Xa level monitoring, as well as peripartum anticoagulation management around labor and delivery.

LEARNING OBJECTIVES
• Describe the practice variation and limited data in the area of postpartum VTE prevention
• Describe management of VTE in pregnancy and an approach to anticoagulation management around labor and delivery

CLINICAL CASE 1
You are seeing a 30-year-old G1P0 woman who is 32 weeks pregnant and is known to be heterozygous for the factor V Leiden gene mutation. She has no personal history of venous thromboembolism (VTE), but her mother has a history of an unprovoked VTE. She has no other VTE risk factors (RFs) or medical history. She is referred to you for counseling relating to the role of postpartum thromboprophylaxis.

CLINICAL CASE 2
A 25-year-old G2P2 woman had an urgent unplanned cesarean delivery (CD) overnight because of failure to progress in labor. Her CD was uncomplicated, and she had an estimated blood loss of 750mL. Should the patient receive postpartum thromboprophylaxis?

There is an increased risk of VTE (deep vein thrombosis [DVT] and pulmonary embolism [PE]) during pregnancy that affects approximately 1.2 per 1000 deliveries, which is a 5- to 10-fold increased risk compared with the nonpregnant population.1-3 The antepartum period and postpartum period each carry a similar VTE risk (0.6 per 1000 deliveries).1 VTE is a leading cause of direct maternal mortality and can have important long-term consequences, including postthrombotic syndrome, post-PE syndrome associated with functional limitations, and a reduced quality of life.5-6 One of the greatest predictors of postthrombotic syndrome after a pregnancy-associated VTE is having a postpartum DVT.3

The risk of VTE during pregnancy and the postpartum period is higher in patients with additional VTE RFs, such as an inherited thrombophilia or pregnancy-related RFs (eg, a woman with a combination of prolonged antepartum immobility and elevated body mass index ≥25kg/m² has an adjusted odds ratio of 40 to develop a postpartum VTE).10,11 Because the VTE incidence in the postpartum period is still relatively low (even in these higher-risk groups) and large randomized controlled trials have been difficult to conduct,
clinical practice guideline recommendations regarding thromboprophylaxis are largely based on observational data and expert opinion. Information about the VTE risk, bleeding risk, other downsides of low-molecular-weight heparin, related mortality, and patient preferences are taken into account when formulating guideline recommendations.12

LMWH thromboprophylaxis is indicated during pregnancy for individuals with a prior unprovoked or hormone-associated VTE, and LMWH thromboprophylaxis is indicated in the 6-week postpartum period for individuals with any prior VTE (including unprovoked, hormone-associated, or provoked VTE).13 In patients without a personal history of VTE, there is more uncertainty about the role of thromboprophylaxis. There is general guideline agreement (but not complete consensus) on LMWH thromboprophylaxis for an individual with a potential thrombophilia. There are more differences across clinical practice guidelines for the role of LMWH use between suggested LMWH use and clinical practice guidelines for individuals who have a more common inherited thrombophilia (eg, heterozygous factor V Leiden) or those with pregnancy-related RFs (eg, preeclampsia, urgent CD, postpartum hemorrhage).31-34

LMWH thromboprophylaxis recommendations differ across clinical practice guidelines for patients with inherited thrombophilia and are outlined in Table 3 of the 2018 American Society of Hematology (ASH) guidelines for management of VTE in the context of pregnancy.13 There has been less emphasis placed on the role and practice variation of LMWH thromboprophylaxis for pregnancy-related RFs, including after CD. A summary of thromboprophylaxis guideline statements for LMWH use post-CD is listed in Table 1. In a US database that captured over 1.2 million women post-CD, the proportion of patients who would have theoretically received LMWH thromboprophylaxis based on VTE RFs was 0.3%, 16.2%, 73.4%, and 0.2%, according to differing recommendations by the 2011 American College of Obstetricians and Gynecologists (ACOG), 2012 American College of Chest Physicians (ACCP), 2015 Royal College of Obstetricians and Gynaecologists (RCOG), and the 2018 ASH guidelines, respectively27 (Table 2). Similarly, in a retrospective review in Geneva, Switzerland, of 344 postpartum women who delivered in 1 month at 1 center, the theoretical use of postpartum LMWH thromboprophylaxis after CD included 35% (ACOG), 40% (ACCP), 89% (RCOG), and 0% (ASH) (Table 2 for all deliveries). For both examples, the ASH guidelines do not focus on this specific area of recommendation.21

Why do clinical practice guidelines differ? The somewhat obvious answer is because lower-quality evidence is available to inform decisions, which includes the limited data on the actual benefits and risks of thromboprophylaxis in this population. In an updated Cochrane systematic review of available randomized trials, the limited evidence remains “very uncertain about the benefits and harms of VTE thromboprophylaxis” during pregnancy and the postpartum period.24 More specifically, there are differences in how the limited data are interpreted, which can lead to different guideline recommendations. This includes issues of publication date, what statistical strategies are used to combine multiple VTE RFs together, what VTE risk threshold is set to recommend LMWH, if a VTE scoring system is used, and the role of expert and patient opinion.11,25 When should older clinical practice guidelines be considered “retired”? Earlier guidelines, such as those from the ACCP and the Australian and New Zealand Journal of Obstetrics and Gynaecology (ANZ/JOG), were published almost 10 years ago, and so data used to inform decisions may be out of date.10,17 Experts do not agree on what VTE risk threshold to use, which is highlighted in the clinical practice guideline methodology described.13,23 Although most absolute VTE risk thresholds in guidelines (if reported at all) are set somewhere between 1% and 3% to consider LMWH use, some experts have recommended a lower VTE threshold of 0.2% post-CD based on decision modeling.27 Others argue that setting a higher VTE threshold or number needed to treat is required to balance a higher bleeding case fatality rate (compared with the VTE case fatality rate) or other complications seen, which is primarily extrapolated from non-pregnancy data.22,28,29 Understanding what matters to patients is still poorly understood. Bates et al30 interviewed pregnant patients and identified that patients placed similar health state values on recurrent VTE and obstetric bleeding, but this also varied among individuals. Furthermore, how patient values and preferences are incorporated into the guideline recommendations remains variable and unclear, and further work is needed in this area.

Even after making statistical assumptions about the limited data and deciding on a VTE risk threshold to recommend LMWH, we are still learning how this risk is reflected in real-life practice. For example, the 2018 ASH guideline panel recommended a 1% VTE risk threshold for postpartum LMWH use.13 In a large US database study of over 1.2 million cesarean deliveries, patients who were identified as “elevated risk” by the 2018 ASH guidelines had an actual VTE incidence of 20.0 (16.9-25.7) per 1000 cesarean deliveries (2% risk) at 6 weeks postpartum, whereas other clinical practice guidelines “high-risk” categories had lower actual VTE incidences (Table 2).24 In contrast, in a single-center study, the highest calculated VTE risk was approximately 0.5% using a risk score derived by Sultan et al, which is lower than the VTE risk threshold cutoff suggested by the ASH guidelines.33

There have been pregnancy and postpartum VTE risk scores derived and externally validated from large registry databases, but these scores have yet to be studied prospectively or incorporated into guidelines.31-33 Several limitations exist in cohort and database studies, including different RF and VTE definitions used in administrative databases, missing data for some VTE RFs, low numbers of patients with high-risk conditions, and, most important, the actual LMWH prophylaxis use is often not accurately captured.

Although estimating what the true benefit of LMWH is remains unknown, what is equally challenging is estimating the bleeding risk and possible wound complications, cost, and burden of LMWH injections. Introducing an anticoagulant post-CD may theoretically affect wound healing of the incision by causing localized bleeding, but little data remain in this area. In a large retrospective cohort study of 24 229 deliveries, VTE and bleeding outcomes were assessed before and after a standardized thromboprophylaxis hospital protocol was implemented. There was 1.2% and 15.6% of anticoagulant use before and after protocol implementation, respectively. There were no differences in VTE rates seen before and after protocol implementation, but there was a 2-fold higher rate of superficial wound hematomas.22 With competing risks and possible complications, understanding the patient perspective on LMWH use, as well as how we best communicate the benefit and risk of LMWH to our patients, is still needed.

Two pilot trials were conducted that assessed the feasibility of randomizing postpartum women with VTE RFs to LMWH.
### Table 1. LMWH prophylaxis recommendations across major clinical practice guidelines after cesarean delivery

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ASH 2018&lt;sup&gt;36&lt;/sup&gt;</th>
<th>RCOG 2015&lt;sup&gt;26&lt;/sup&gt;</th>
<th>SOGC 2014&lt;sup&gt;18&lt;/sup&gt;</th>
<th>ACCP 2012&lt;sup&gt;15&lt;/sup&gt;</th>
<th>ANZJOG 2012&lt;sup&gt;17&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective</td>
<td>CD alone</td>
<td>No</td>
<td>No</td>
<td>For women undergoing cesarean section without additional thrombosis RFs, we recommend against the use of thrombosis prophylaxis other than early mobilization (grade 1B).</td>
<td></td>
</tr>
<tr>
<td>Emergent</td>
<td>CD alone</td>
<td>No</td>
<td>No</td>
<td>No; early mobilization and avoidance of dehydration Following emergency cesarean section thromboprophylaxis with LMWH or UFH is recommended for at least 5 days or longer until recovery of full mobility (group consensus level 1).</td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>CD + RF</td>
<td>Not stated</td>
<td>See above; considered for thromboprophylaxis with LMWH for 10 days after delivery (grade C).</td>
<td>Postpartum thromboprophylaxis should be considered in the presence of multiple clinical or pregnancy-related RFs when the overall absolute risk is estimated to be greater than 1% drawn from the following groupings: Any 2 of the following RFs (emergency cesarean section counts as 1 RF) (II-2B) LMWH until discharge up to 2 weeks if 2 RFs</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For women at increased risk of VTE after cesarean section because of the presence of 1 major or at least 2 minor RFs, we suggest pharmacologic thromboprophylaxis (prophylactic LMWH) or mechanical prophylaxis (elastic stockings or intermittent pneumatic compression) in those with contraindications to anticoagulants while in the hospital following delivery rather than no prophylaxis (grade 2B).</td>
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Emergent CD + RF

All women who have had cesarean sections should be considered for thromboprophylaxis with LMWH for 10 days after delivery apart from those having an elective cesarean section who should be considered for thromboprophylaxis with LMWH for 10 days after delivery if they have any additional RFs (grade C).

Postpartum thromboprophylaxis should be considered in the presence of multiple clinical or pregnancy-related RFs when the overall absolute risk is estimated to be >1% drawn from the following groupings: Any 3 or more of the following RFs (elective cesarean section counts as 1 RF) (II-2B)

LMWH until discharge up to 2 weeks if 1 RF

Further details in Table 3: Requires presence of at least 1 major RF OR presence of at least 2 minor RFs (planned cesarean section) OR 1 minor RF in the setting of an emergency cesarean section

Note: These mostly include pregnancy-related RFs and do not review inherited thrombophilia guidance unless stated below.

ACCP: Major RFs: Immobility, postpartum hemorrhage ≥1000mL with surgery, previous VTE, preeclampsia with fetal growth restriction, thrombophilia (AT deficiency, factor V Leiden, prothrombin gene mutation), medical conditions (SLE, heart disease, sickle cell disease), blood transfusion, postpartum infection. Minor RFs: BMI >30kg/m², multiple pregnancy, PPH >1L, smoking >10 cigarettes/d, fetal growth restriction, thrombophilia (protein C and S deficiency), preeclampsia.

RCOG: See Table 1 of the 2015 RCOG guidelines.

SOGC: Any 2 of the following RFs: BMI ≥30kg/m², smoking >10 cigarettes/d, preeclampsia, intrauterine growth restriction, placenta previa, emergency cesarean section, peripartum or postpartum blood loss of >1L or blood product replacement, any low-risk thrombophilia (protein C or protein S deficiency), heterozygous factor V Leiden, or prothrombin gene mutation 20210A, maternal cardiac disease, SLE, sickle cell disease, inflammatory bowel disease, varicose veins, gestational diabetes, preterm delivery, stillbirth. Any 3 or more of the following RFs: age >35 years, parity ≥2, any assisted reproductive technology, multiple pregnancy, placental abruption, premature rupture of membranes, elective cesarean section, maternal cancer. ANZJOG: Major RFs: Elective cesarean section, BMI ≥30kg/m², immobilization, medical comorbidity (eg, inflammatory bowel disease, SLE, pneumonia), preeclampsia, systemic infection. Minor RFs: Age >35 years, prolonged labor (>24 hours), smoker, PPH >1000mL, extensive perineal trauma and prolonged repair, gross varicose veins.

Table 1 (continued)

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<tbody>
<tr>
<td>Emergent CD + RF</td>
<td>Not stated</td>
<td>All women who have had cesarean sections should be considered for thromboprophylaxis with LMWH for 10 days after delivery apart from those having an elective cesarean section who should be considered for thromboprophylaxis with LMWH for 10 days after delivery if they have any additional RFs (grade C).</td>
<td>Postpartum thromboprophylaxis should be considered in the presence of multiple clinical or pregnancy-related RFs when the overall absolute risk is estimated to be &gt;1% drawn from the following groupings: Any 3 or more of the following RFs (elective cesarean section counts as 1 RF) (II-2B)</td>
<td>Further details in Table 3: Requires presence of at least 1 major RF OR presence of at least 2 minor RFs (planned cesarean section) OR 1 minor RF in the setting of an emergency cesarean section</td>
<td>Following emergency cesarean section, thromboprophylaxis with LMWH or UFH is recommended for at least 5 days or longer until recovery of full mobility (group consensus level 1).</td>
</tr>
</tbody>
</table>

Note: These mostly include pregnancy-related RFs and do not review inherited thrombophilia guidance unless stated below.

ACCP: Major RFs: Immobility, postpartum hemorrhage ≥1000mL with surgery, previous VTE, preeclampsia with fetal growth restriction, thrombophilia (AT deficiency, factor V Leiden, prothrombin gene mutation), medical conditions (SLE, heart disease, sickle cell disease), blood transfusion, postpartum infection. Minor RFs: BMI >30kg/m², multiple pregnancy, PPH >1L, smoking >10 cigarettes/d, fetal growth restriction, thrombophilia (protein C and S deficiency), preeclampsia.

RCOG: See Table 1 of the 2015 RCOG guidelines.

SOGC: Any 2 of the following RFs: BMI ≥30kg/m², smoking >10 cigarettes/d, preeclampsia, intrauterine growth restriction, placenta previa, emergency cesarean section, peripartum or postpartum blood loss of ≥1L or blood product replacement, any low-risk thrombophilia (protein C or protein S deficiency), heterozygous factor V Leiden, or prothrombin gene mutation 20210A, maternal cardiac disease, SLE, sickle cell disease, inflammatory bowel disease, varicose veins, gestational diabetes, preterm delivery, stillbirth. Any 3 or more of the following RFs: age >35 years, parity ≥2, any assisted reproductive technology, multiple pregnancy, placental abruption, premature rupture of membranes, elective cesarean section, maternal cancer. ANZJOG: Major RFs: Elective cesarean section, BMI ≥30kg/m², immobilization, medical comorbidity (eg, inflammatory bowel disease, SLE, pneumonia), preeclampsia, systemic infection. Minor RFs: Age >35 years, prolonged labor (>24 hours), smoker, PPH >1000mL, extensive perineal trauma and prolonged repair, gross varicose veins.

ASH 2018: The panel used the GRADE approach to assess the certainty in the evidence and formulate recommendations.

RCOG 2015: Described in a separate methodology article: “using the SIGN methodology, the quality of the evidence used and the directness of its application should be incorporated into the formulation and grading of the recommendation.”

SOGC 2014: “The quality of evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventative Health Care.”

ACCP 2012: “We followed the approach articulated by Grades of Recommendations, Assessment, Development, and Evaluation for formulation of recommendations.”

ANZJOG 2012: “To assess the level of consensus with the recommendations, all authors were sent a spreadsheet listing all the recommendations and were asked to indicate whether they agreed or disagreed with each statement. Recommendations were then graded with the following levels of consensus: Group Consensus Level 1—complete consensus: all ten authors in agreement; Group Consensus Level 2—partial consensus: eight of ten authors in agreement; Group Consensus Level 3—no consensus—two or more authors disagreed with recommendation.”

AT, antithrombin; BMI, body mass index; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; PPH, postpartum hemorrhage; SLE, systemic lupus erythematosus; SOGC, Society of Obstetricians and Gynaecologists of Canada.
Table 2. Differences in clinical practice guidelines for the use of postpartum thromboprophylaxis and associated VTE risk

<table>
<thead>
<tr>
<th>Author, year, and location</th>
<th>Population</th>
<th>n (% who underwent CD)</th>
<th>Proportion meeting criteria for LMWH prophylaxis</th>
<th>Statements of actual LMWH use</th>
<th>Incidence of VTE in women who met guideline criteria for LMWH prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamerola, 192016, USA</td>
<td>Post-CD; cross-sectional chart review at 2 time points in 2013-2014</td>
<td>293 CD: 100%</td>
<td>ACOG: 1.0% RCOG: 85% ACCP: 34.8%</td>
<td>“At the centre where this study was performed, heparin is administered empirically to all women after CD unless there is a specific contraindication.”</td>
<td>NR</td>
</tr>
<tr>
<td>Omunakwe, 2016, UK</td>
<td>All deliveries; 4 weeks in September-October 2015</td>
<td>227 CD: 35%</td>
<td>RCOG: 46.6%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>O'Shaughnessy, 2019, Ireland</td>
<td>All deliveries; cross-sectional study of prospectively collected data; January 2015 to December 2017</td>
<td>21 019 CD: 32%</td>
<td>ACOG: 8% RCOG: 37% ACCP: 7% Australia/New Zealand: 23% SOGC: 15%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Federspiel et al, 2021, USA</td>
<td>Post-CD; Nationwide Readmissions Database, October 2015 to December 2017</td>
<td>1 390 603 CD: 100%</td>
<td>ACOG: 0.3% RCOG: 73.4% ACCP: 16.2% ASH: 0.2%*</td>
<td>Unknown</td>
<td>VTE incidence per 1000 deliveries: ACOG: 19.5 (14.9-23.9) RCOG: 19 (1.8-20.0) ACCP: 6.2 (3.9-4.6) ASH: 20.0 (14.9-25.7)</td>
</tr>
<tr>
<td>Gassmann et al, 2021, Switzerland</td>
<td>All deliveries in January 2019; retrospective chart review</td>
<td>344 CD: 23.3%</td>
<td>ACOG: 8.7% RCOG: 40.1% (34.9%-45.5%) ACCP: 9.9% ASH: 0%*</td>
<td>24% “Standard of care is to prescribe thromboprophylaxis to women with CD. For women with vaginal delivery, LMWH is restricted to those with thrombophilia or prior VTE, following individual hemostasis consultation.”</td>
<td>Calculated based on Sultan risk score: ACOG: 0.20% RCOG: 0.12% ACCP: 0.20%;</td>
</tr>
</tbody>
</table>

*The 2018 ASH guidelines did not specifically comment on post-CD thromboprophylaxis use (see Table 1). NR, not reported.

vs placebo/no LMWH for 10 to 21 days. Unfortunately, both pilot trials were not feasible due to low participant recruitment rates that averaged <1 participant enrolled per month per center. In a survey of 306 patients who were eligible but did not participate, 32% were too overwhelmed or preoccupied in the postpartum period to consider research, and 28.4% declined because they wanted to avoid LMWH injections. Although participant numbers were too small in the pilot PROSPER (PostpaRtum Prophylaxis for PE Randomized Control Trial Pilot) trials to comment on the efficacy or safety of postpartum LMWH use, there was 1 major bleeding event and 2 clinically relevant nonmajor bleeding events among 16 participants, which highlights that high-quality trials are still needed to determine the true risk and benefit of postpartum thromboprophylaxis. The pilot PARTUM (Postpartum Aspirin to Reduce Thromboembolism Undue Morbidity) trial is ongoing, to see the feasibility of low-dose aspirin for 6 weeks to prevent VTE in postpartum women with VTE RFs, compared with placebo (clinicaltrials.gov ID NCT04153760).

CLINICAL CASE 1 (Continued)

Given the limited data in this area, the patient should be approached to participate in a research study such as the pilot PARTUM trial. In the absence of an available research study, the 2018 ASH guideline panel suggests against thromboprophylaxis use for this patient, even with the presence of a family history of VTE. Because other clinical practice guidelines recommend thromboprophylaxis in this scenario, further discussion is needed with the patient before making an informed decision, including highlighting this practice variation and reviewing the patient’s values and preferences. Regardless of the choice to use LMWH or not postpartum, symptoms of VTE and when to seek medical attention should be reviewed. A review of additional pregnancy-related RFs should also be completed at the time of delivery.

CLINICAL CASE 2 (Continued)

The absolute risk of postpartum VTE after urgent CD is less than 1%, and it is still uncertain what the true benefit of LMWH thromboprophylaxis is in this situation, weighing the side effects and system-level cost. Although I would not recommend LMWH thromboprophylaxis in this case, others would recommend LMWH use, such as in the 2015 RCOG guidelines. Instead, I would advocate for early mobilization and reassess the role of LMWH if additional postpartum VTE RFs develop.
Management of VTE in pregnancy

CLINICAL CASE 3

You are seeing a 29-year-old G2P1 woman who developed a symptomatic PE at 20 weeks' gestation based on a high-probability V/Q scan with large mismatched defects in the left lower lobe. Her vitals are normal, and she has no examination findings of DVT. Her pregnancy has been unremarkable, and she has no other medical history. Her only medication is a prenatal vitamin. What anticoagulant regimen do you recommend for her pregnancy?

Therapeutic-dose LMWH is the recommended treatment for pregnant patients with acute VTE because it does not cross the placenta and has an improved safety profile compared with unfractionated heparin (UFH). Vitamin K antagonists are not recommended in pregnancy due to known teratogenicity, and direct oral anticoagulants still have limited safety information (with an International Society on Thrombosis and Haemostasis direct oral anticoagulants still have limited safety information) ongoing).37,38 Side effects of LMWH use during pregnancy include a small risk of important bleeding antepartum (~0.5%), injection site bruising and reactions, and a very rare possibility of heparin-induced thrombocytopenia.39 Unlike UFH, prophylactic or intermediate-dose LMWH does not reduce bone mineral density during pregnancy, but less data are available for therapeutic doses.50,51 Systemic thrombolysis should only be reserved for patients with PE who have life-threatening hemodynamic compromise or cardiac arrest given the excessive bleeding risk (among 83 women treated with systemic thrombolysis: maternal survival, 94%; fetal survival, 88%; antepartum major bleeding, 17.5%; postpartum major bleeding, 58.3%).52 Beyond these statements, there remains significant practice variation on the details of anticoagulation management in pregnancy.53

As pregnancy advances, there is an increased volume of distribution and glomerular filtration rate, so there is the potential for increased clearance of LMWH.54,55 Because of these pregnancy-specific changes, there remains controversy on the use of once- vs twice-daily LMWH dosing and the role of anti-Xa level monitoring of LMWH. In a 2014 Canadian survey of 69 hematologists, internists, and obstetricians, there was considerable practice variation in acute VTE management. Within the first month of a VTE event, participants used either once-daily (36%) or twice-daily (62%) LMWH, and anti-Xa level monitoring was completed weekly (20%), monthly (26%), weekly or monthly in special populations only (23%), or never (20%).10

A systematic review in nonpregnant patients showed similar outcomes of once- vs twice-daily LMWH dosing.15 To date, there has been no clear outcome difference in recurrent VTE seen in retrospective cohorts of pregnant patients treated with different regimens.10 Information related to anti-Xa level monitoring is limited to small cohorts of pregnant patients who received different therapeutic-dose LMWH regimens in which physicians titrated LMWH doses based on various anti-Xa level targets; no major safety signals were identified across different strategies, albeit with limited data from a small number of patients.10,54 One challenge in interpreting anti-Xa levels is that a specific “anti-Xa level range” in pregnancy is not known, because there is no data available to correlate anti-Xa levels with VTE or bleeding outcomes. In the largest non-randomized study of 26 participants (11 received anti-Xa level monitoring and 15 did not receive anti-Xa level monitoring), there was no difference in recurrent VTE or bleeding reported.53 Based on limited evidence, the 2018 ASH guideline panel suggests either a once-daily or twice-daily LMWH regimen be used and suggested against anti-Xa level monitoring with the potential exception of higher-risk scenarios, such as in those patients with obesity or advanced renal dysfunction.15 Table 3 summarizes various clinical practice guideline recommendations for once- vs twice-daily LMWH, anti-Xa level monitoring, and peripartum anticoagulation management (discussed further in case 4).

CLINICAL CASE 3 (Continued)

Whatever anticoagulant regimen is chosen, it is important to have close follow-up and monitoring of symptoms, especially in the first month of treatment. The recommendations presented by the 2018 ASH guidelines are a patient-focused approach that includes minimizing the number of injections and laboratory visits. Although this aligns with my general practice and approach for the majority of patients, I would consider escalating to a twice-daily LMWH and/or anti-Xa level monitoring in the first month of VTE treatment in those with higher-risk features, such as those with extensive VTE burden, recurrent VTE despite anticoagulation, or patients with a high-risk thrombophilia such as antiphospholipid syndrome.

Peripartum management of anticoagulation

CLINICAL CASE 4

A 38-year-old G0 woman had a large PE 2 years ago after starting a combined oral contraceptive pill. After receiving 6 months of anticoagulation, she stopped anticoagulation and the contraceptive pill and had a progesterone-only intruterine device placed. She is now interested in getting pregnant. You meet her for a preconception counseling visit and recommended starting prophylactic-dose LMWH during pregnancy and the 6-week postpartum period to prevent recurrent VTE. She has several questions about what this means for her delivery and if she will be able to get an epidural for pain control.

One of the more challenging areas with little high-quality data is when and how to stop anticoagulation around labor and delivery, as well as when to resume postpartum anticoagulation. Systematic reviews report the variable and low-quality retrospective data available that physicians rely on to make decisions about anticoagulant management.57,58,59. One particular challenge in the literature has been the different definitions of peripartum bleeding; peripartum bleeding definitions may be based on estimated blood loss alone (variably measured across centers), a decrease in hemoglobin, blood transfusion, hospital readmissions, repeat surgery, or wound complications.57,62 To minimize this variation, the International Society on Thrombosis and Haemostasis Committee of Women’s Health Issues in Thrombosis...
Table 3. Recommendations of VTE management in pregnancy across major clinical practice guidelines

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<tbody>
<tr>
<td>Once- vs twice-daily LMWH</td>
<td>For pregnant women with acute VTE treated with LMWH, the ASH guideline panel suggests either once-per-day or twice-per-day dosing regimens (conditional recommendation, very low certainty in evidence about effects).</td>
<td>LMWH should be given in doses titrated against the woman's booking or early pregnancy weight. There is insufficient evidence to recommend whether the dose of LMWH should be given once daily or in two divided doses (grade C).</td>
<td>For the treatment of acute VTE in pregnancy, we recommend adhering to the manufacturer's recommended dosing for individual LMWH based on the woman's current weight. (II-1A). LMWH can be administered once or twice a day depending on the agent selected (II-C).</td>
<td>No recommendation</td>
<td>Treatment of acute VTE in pregnancy should be with LMWH given once daily or twice daily at therapeutic doses. There is currently insufficient evidence to favor one dose regimen over the other (group consensus level 1). Women with PE or more extensive DVT (ie, iliofemoral thrombosis) during pregnancy should receive initial treatment with twice-daily LMWH for at least 8 to 12 weeks, after which time a reduction to a once-daily regimen may be considered (group consensus level 2).</td>
</tr>
<tr>
<td>Anti-Xa level monitoring</td>
<td>For pregnant women receiving therapeutic-dose LMWH for the treatment of VTE, the ASH guideline panel suggests against routine monitoring of anti-FXa levels to guide dosing (conditional recommendation, low certainty in evidence about effects).</td>
<td>Routine measurement of peak anti-Xa activity for patients taking LMWH for treatment of acute VTE in pregnancy or postpartum is not recommended except in women at extremes of body weight (&lt;50 and 90 kg or more) or with other complicating factors (eg, with renal impairment or recurrent VTE) (grade C).</td>
<td>No recommendation</td>
<td>No recommendation</td>
<td>There is insufficient evidence to recommend monitoring of anti-Xa levels to guide dosing in women on therapeutic dose LMWH (group consensus level 1).</td>
</tr>
</tbody>
</table>

[^5]: Downloaded from This publication as a reference for the website.
For pregnant women receiving therapeutic-dose LMWH for the management of VTE, the ASH guideline panel suggests scheduled delivery with prior discontinuation of anticoagulant therapy (conditional recommendation, very low certainty in evidence about effects).

For pregnant women receiving prophylactic-dose LMWH, the ASH guideline panel suggests against scheduled delivery with discontinuation of prophylactic anticoagulation compared with allowing spontaneous labor (conditional recommendation, very low certainty in evidence about effects).

The woman taking LMWH for maintenance therapy should be advised that once she is in established labor or thinks that she is in labor, she should not inject any further heparin. When VTE occurs at term, consideration should be given to the use of intravenous UFH, which is more easily manipulated (grade D).

Where delivery is planned, either by elective cesarean section or induction of labor, LMWH maintenance therapy should be discontinued 24 hours prior to planned delivery (grade D).

Women receiving prophylactic, intermediate-dose, or therapeutic anticoagulation should have a discussion about options for analgesia/anesthesia prior to delivery (III-B).

Switching from thromboprophylactic LMWH to a prophylactic dose of UFH at term (37 weeks) may be considered to allow for more options with respect to labor analgesia (III-L).

Discontinue prophylactic or intermediate-dose LMWH or UFH upon the onset of spontaneous labor or the day before a planned induction of labor or cesarean section (III-B).

For pregnant women receiving adjusted-dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 hours prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (grade 1B).

No recommendation

Table 3. (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ASH 2018&lt;sup&gt;15&lt;/sup&gt;</th>
<th>RCOG 2015&lt;sup&gt;13&lt;/sup&gt;</th>
<th>SOGC 2014&lt;sup&gt;16&lt;/sup&gt;</th>
<th>ACCP 2012&lt;sup&gt;17&lt;/sup&gt;</th>
<th>ANZiOG 2012&lt;sup&gt;18&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripartum anticoagulation management</td>
<td>For pregnant women receiving therapeutic-dose LMWH for the management of VTE, the ASH guideline panel suggests scheduled delivery with prior discontinuation of anticoagulant therapy (conditional recommendation, very low certainty in evidence about effects).</td>
<td>The woman taking LMWH for maintenance therapy should be advised that once she is in established labor or thinks that she is in labor, she should not inject any further heparin. When VTE occurs at term, consideration should be given to the use of intravenous UFH, which is more easily manipulated (grade D). Where delivery is planned, either by elective cesarean section or induction of labor, LMWH maintenance therapy should be discontinued 24 hours prior to planned delivery (grade D).</td>
<td>Women receiving prophylactic, intermediate-dose, or therapeutic anticoagulation should have a discussion about options for analgesia/anesthesia prior to delivery (III-B). Switching from thromboprophylactic LMWH to a prophylactic dose of UFH at term (37 weeks) may be considered to allow for more options with respect to labor analgesia (III-L). Discontinue prophylactic or intermediate-dose LMWH or UFH upon the onset of spontaneous labor or the day before a planned induction of labor or cesarean section (III-B).</td>
<td>For pregnant women receiving adjusted-dose LMWH therapy and where delivery is planned, we recommend discontinuation of LMWH at least 24 hours prior to induction of labor or cesarean section (or expected time of neuraxial anesthesia) rather than continuing LMWH up until the time of delivery (grade 1B).</td>
<td></td>
</tr>
<tr>
<td>Time of neuraxial anesthesia after last dose of LMWH</td>
<td>Regional anesthetic or analgesic techniques should not be undertaken until at least 24 hours after the last dose of therapeutic LMWH (grade D).</td>
<td>For women taking LMWH, neuraxial anesthesia can be administered as: (a) Prophylactic dose: a minimum of 10 to 12 hours after the last dose (II-B) (b) Therapeutic dose: after 24 hours since the last dose (II-B) Neuraxial anesthesia must be avoided in a woman who is fully anticoagulated or in whom there is evidence of altered coagulation (II-3A).</td>
<td></td>
<td></td>
<td>PVC 2010&lt;sup&gt;19&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

See Table 1 for descriptions used for evidence grading and consensus.
and Haemostasis developed and published standardized pregnancy and peripartum bleeding outcome definitions, which focus on the interventions needed to treat important blood loss rather than on estimated blood loss alone.63

There is controversy on what to do for a patient taking prophylactic-dose LMWH because there is a relatively low bleeding risk, and access to neuraxial anesthesia can occur 12 hours after the last anticoagulant dose, according to several guidelines, including the American Society of Regional Anesthesia and the Society for Obstetric Anesthesia and Perinatology (Table 3).54,65 The 2018 ASH guideline panel suggests a spontaneous labor over a timed induction of labor for pregnant patients taking prophylactic-dose LMWH, but acknowledging this decision is also based on individual patient values and preferences.13 In a retrospective cohort study of 199 patients taking prophylactic-dose LMWH in pregnancy, approximately 90% of those in spontaneous labor were eligible for neuraxial anesthesia, which did not differ based on if the patient was primiparous (first pregnancy) or multiparous.64 In this retrospective study, there was notably less time off of anticoagulation for patients in the spontaneous labor group compared with the induction of labor group (last LMWH injection to delivery interval: 25.8 vs 48.2 hours, respectively).64 If a patient values access to neuraxial anesthesia for pain control, then other options include a planned induction of labor or stopping LMWH early depending on the scenario and associated VTE risk. For example, the last dose of LMWH can be given the day prior to an induction of labor to ensure that at least 12 hours have passed since the last anticoagulant dose was given for the patient to be eligible for neuraxial anesthesia. However, in practice, this is often challenging because the induction of labor timing may not be known until the actual day due to hospital logistics, and the induction of labor duration is often variable and can be prolonged in some patients. A discussion between multidisciplinary care providers can be helpful to coordinate logistics and the details of the induction of labor, to provide accurate risks and benefits of each approach with the patient.

For patients receiving therapeutic-dose LMWH, because of the potential for excess bleeding risk during delivery and delayed access to neuraxial anesthesia of 24 hours after the last LMWH dose,54,65 the 2018 ASH guideline panel recommends a planned labor (eg, induction of labor), with the last dose of LMWH given 24 hours prior to induction/delivery.13 If the VTE is not acute (>3-6 months), then an alternative approach (albeit with limited data) includes reducing the LMWH dose closer to delivery from a therapeutic dose to a prophylactic dose, to allow for spontaneous delivery. If the VTE is within 2 weeks of delivery, then using a more cautious anticoagulant regimen may be considered to minimize time off of anticoagulation, such as starting or switching to a twice-daily LMWH or arranging admission to the hospital for intravenous UFH. An inferior vena cava (IVC) filter insertion may be considered if the VTE is within 2 weeks of delivery, but this is largely based on expert opinion. IVC filter insertion should otherwise be avoided when possible due to the challenges of insertion and possible migration relating to the gravid uterus and IVC changes, and the decision should be made in consultation with a multidisciplinary specialist team. The failure-to-retrieve rate of IVC filters among 80 pregnant patients was 11.3%, so it is important to remove the IVC filter after delivery once anticoagulation is safely resumed.67

Two multicenter international prospective cohort studies are ongoing (PREP and GO and the PANDA studies) and will use standardized VTE and bleeding definitions to provide more information on the risk estimates of VTE, bleeding, patient-focused and health care utilization outcomes that matter to patients, providers, and other stakeholders.

Postpartum, retrospective cohort data report an increased bleeding risk if therapeutic-dose anticoagulation is resumed too soon after delivery. Initiating therapeutic-dose LMWH too soon may lead to serious postoperative bleeding complication in which the patient may be off of anticoagulation for longer, which could then increase the risk of VTE. In a retrospective cohort study of 232 consecutive women on therapeutic anticoagulation who delivered in Quebec, Canada, between 2003 and 2015, resuming therapeutic anticoagulation within approximately 15 hours64 after CD and approximately 9 hours within vaginal delivery was associated with a higher risk of a composite of major hemorrhagic complications (requiring transfusion, hospitalization, volume resuscitation, transfer to an intensive care unit, or surgery) and major wound complications. Starting with a prophylactic-dose LMWH postdelivery or delaying therapeutic anticoagulation for longer appears safer. Practically, for most patients, resuming daily prophylactic-dose LMWH the following day after delivery (~12-24 hours postdelivery) can be done, such as for case 4. I follow the approach of starting with prophylactic-dose LMWH before escalating to therapeutic-dose LMWH on day 2 or 3 postdelivery if needed. For higher-risk cases, such as an acute VTE within 30 days, this approach should be modified and may include starting with twice-daily LMWH or intravenous UFH 6 to 12 hours postdelivery. Postpartum, either LMWH or vitamin K antagonists are safe with breastfeeding. Data indicate that direct oral anticoagulants cross into breastmilk and should be avoided for breastfeeding women until more data are available.69-70

Conflict-of-interest disclosure
Leslie Skeith has received research funding from CSL Behring, and honorarium from Leo Pharma and Sanofi.

Off-label drug use
Leslie Skeith: the use of low-molecular-weight heparins is off-label use for the prevention and treatment of VTE during pregnancy and the postpartum period. The use of aspirin for prevention of postpartum VTE is off-label and should only be used in the setting of a clinical trial.

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