



ASH CLINICAL PRACTICE GUIDELINES  
VENOUS THROMBOEMBOLISM (VTE)



# Venous Thromboembolism in the Context of Pregnancy

## *An Educational Slide Set*

American Society of Hematology 2018 Guidelines  
for Management of Venous Thromboembolism

### **Slide set authors:**

Eric Tseng MD MScCH, University of Toronto  
Shannon Bates MDCM MSc, McMaster University



# American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy

Shannon M. Bates, Anita Rajasekhar, Saskia Middeldorp, Claire McLintock, Marc A. Rodger, Andra H. James, Sara R. Vazquez, Ian A. Greer, John J. Riva, Meha Bhatt, Nicole Schwab, Danielle Barrett, Andrea LaHaye, and Bram Rochwerg

## American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy

Shannon M. Bates,<sup>1,2</sup> Anita Rajasekhar,<sup>3</sup> Saskia Middeldorp,<sup>4</sup> Claire McLintock,<sup>5</sup> Marc A. Rodger,<sup>6,8</sup> Andra H. James,<sup>9</sup> Sara R. Vazquez,<sup>10</sup> Ian A. Greer,<sup>11</sup> John J. Riva,<sup>12,13</sup> Meha Bhatt,<sup>14</sup> Nicole Schwab,<sup>15</sup> Danielle Barrett,<sup>16</sup> Andrea LaHaye,<sup>17</sup> and Bram Rochwerg<sup>18,19</sup>

<sup>1</sup>Department of Medicine, Division of Hematology and Thromboembolism, and <sup>2</sup>Thrombosis and Atherosclerosis Research Institute, McMaster University, Hamilton, ON, Canada; <sup>3</sup>Department of Medicine, Division of Hematology and Oncology, University of Florida, Gainesville, FL; <sup>4</sup>Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; <sup>5</sup>National Women's Health, Auckland City Hospital, Auckland, New Zealand; <sup>6</sup>Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada; <sup>7</sup>Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada; <sup>8</sup>Ottawa Blood Disease Centre, The Ottawa Hospital, Ottawa, ON, Canada; <sup>9</sup>Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Duke University, Durham, NC; <sup>10</sup>Department of Pharmacy Services, University of Utah Health Sciences Service, Salt Lake City, UT; <sup>11</sup>Queens University, Belfast, Northern Ireland, United Kingdom; <sup>12</sup>Department of Family Medicine, and <sup>13</sup>Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada; <sup>14</sup>Department of Laboratory Medicine and Pathology, University of Toronto, Toronto, ON, Canada; <sup>15</sup>Patient Representative, Wake Forest, NC; <sup>16</sup>Patient Representative, Alexandria, VA; and <sup>17</sup>Department of Medicine, Division of Critical Care, McMaster University, Hamilton, ON, Canada

**Background** Venous thromboembolism (VTE) complicates ~1.2 of every 1000 deliveries. Despite these low absolute risks, pregnancy-associated VTE is a leading cause of maternal morbidity and mortality.

**Objective** These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians and others in decisions about the prevention and management of pregnancy-associated VTE.

**Methods** ASH formed a multidisciplinary guideline panel balanced to minimize potential bias from conflicts of interest. The McMaster University GRADE Centre supported the guideline development process, including updating or performing systematic evidence reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess evidence and make recommendations.

**Results** The panel agreed on 31 recommendations related to the treatment of VTE and superficial vein thrombosis, diagnosis of VTE, and thrombosis prophylaxis.

**Conclusions** There was a strong recommendation for low-molecular-weight heparin (LMWH) over unfractionated heparin for acute VTE. Most recommendations were conditional, including those for either twice-per-day or once-per-day LMWH dosing for the treatment of acute VTE and initial outpatient therapy over hospital admission with low-risk acute VTE, as well as against routine anti-factor Xa (FXa) monitoring to guide dosing with LMWH for VTE treatment. There was a strong recommendation (low certainty in evidence) for antepartum anticoagulant prophylaxis with a history of unprovoked or hormonally associated VTE and a conditional recommendation against antepartum anticoagulant prophylaxis with prior VTE associated with a resolved nonhormonal provoking risk factor.

### Summary of recommendations

Venous thromboembolism (VTE) complicates ~1.2 of every 1000 deliveries.<sup>1,2</sup> Despite these low absolute risks, pregnancy-associated VTE is a leading cause of maternal morbidity and mortality.<sup>3-6</sup> The diagnosis, prevention, and treatment of pregnancy-associated VTE are particularly difficult because of the need to consider fetal as well as maternal well-being. These guidelines address these challenging issues.

These guidelines are based on updated and original systematic reviews of evidence conducted under the direction of the McMaster University GRADE Centre with international collaborators. The panel



## ASH Clinical Practice Guidelines on VTE

1. Prevention of VTE in Surgical Hospitalized Patients
2. Prevention of VTE in Medical Hospitalized Patients
3. Treatment of Acute VTE (DVT and PE)
4. Optimal Management of Anticoagulation Therapy
5. Prevention and Treatment of VTE in Patients with Cancer
6. Heparin-Induced Thrombocytopenia (HIT)
7. Thrombophilia
8. Pediatric VTE
- 9. VTE in the Context of Pregnancy**
10. Diagnosis of VTE

## How were these ASH guidelines developed?

### PANEL FORMATION

Each guideline panel was formed following these key criteria:

- Balance of expertise (including disciplines beyond hematology, and patients)
- Close attention to minimization and management of COI

### CLINICAL QUESTIONS

10 to 20 clinically-relevant questions generated in **PICO format** (population, intervention, comparison, outcome)

#### Example: PICO question

“Should postpartum prophylaxis vs. no postpartum prophylaxis be used for pregnant women with prior VTE?”

### EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

### MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence for all factors.

***ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.***

## How patients and clinicians should use these recommendations

	<b>STRONG Recommendation</b> ("The panel recommends...")	<b>CONDITIONAL Recommendation</b> ("The panel suggests...")
<b>For patients</b>	Most individuals would want the intervention.	A majority would want the intervention, but many would not.
<b>For clinicians</b>	Most individuals should receive the intervention.	Different choices will be appropriate for different patients, depending on their values and preferences. Use <b>shared decision making</b> .



## Objectives

By the end of this session, you should be able to

1. Describe recommendations for the management of acute VTE in pregnancy
2. Describe which anticoagulants can safely be used in women who are pregnant or breastfeeding
3. Identify which pregnant patients merit antepartum and/or postpartum VTE prophylaxis



## VTE is a leading cause of morbidity and mortality in pregnancy

Venous thrombosis complicates approximately **1.2 in 1,000** deliveries

Incidence of VTE is similar in antepartum and postpartum periods, but **postpartum period shorter so higher daily VTE risk**

Increased risk persists until 12 weeks postpartum, with **greatest risk in first 6 weeks** after delivery

Diagnosis, prevention, and treatment of VTE in pregnancy must consider both **fetal and maternal well-being**



## Case 1: Suspected Deep Vein Thrombosis

32 year old female, 28 weeks gestational age. 1<sup>st</sup> pregnancy.

**Past Medical History:** None. No prior arterial or venous thrombosis.

**Medications:** Prenatal vitamin

### **Seen in the Emergency Department with:**

New swollen and painful left thigh x 48 hours.

No chest pain or dyspnea.

### **Proximal compression ultrasound of the left lower extremity:**

No evidence of DVT in the popliteal, femoral, common femoral, or external iliac veins.





Your patient is 28 weeks pregnant and has unexplained left leg swelling and pain. Her left leg proximal compression ultrasound does not demonstrate proximal DVT. She has no signs or symptoms suggestive of PE.

Which diagnostic test would you suggest next in her care?

- A. No further investigations
- B. D-Dimer test
- C. Serial compression ultrasound (US) of lower extremity
- D. Magnetic resonance venography (MR-V)
- E. Ventilation/Perfusion (V/Q) scan

**Either  
C or D**

## Recommendation

For pregnant women with suspected DVT, the panel suggests **additional investigations including serial compression ultrasound or MR-V**, compared with no further investigations, following an initial negative ultrasound with imaging of the iliac veins (*conditional recommendation, low certainty*).

### Remarks:

- *Standard compression US*: limited sensitivity for pelvic/iliac DVT, which account for majority of DVT in pregnancy
- Single US not sufficient to rule out DVT, as up to 24% of DVT in pregnancy will be found on serial testing (*very uncertain estimates*)

### Option 1: Serial US

Repeating US within 7 days appears to be safe strategy with low rate of missed VTE in observational studies

### Option 2: MR-V

May detect pelvic DVT not seen on compression US. MRI in first trimester not associated with fetal harm.

## Case 1: Continued

- Your patient is discharged and scheduled for a serial compression US in 5 days
- Her **repeat US** demonstrates an occlusive DVT in the left common femoral vein
- She is ambulatory and her pain is persistent, but controlled with acetaminophen

### Examination:

- Blood pressure 120/84
- Heart rate 86
- Respiratory rate 16
- Oxygen saturation 98% on room air
- Left leg warm, with normal pulses and sensation

Your patient is 29 weeks pregnant and has an acute proximal DVT. She is ambulatory and hemodynamically stable.

What anticoagulant therapy would you suggest for her DVT?

*(UFH = unfractionated heparin, LMWH = low molecular weight heparin)*

- A. Subcutaneous UFH
- B. Direct oral anticoagulant
- C. LMWH once or twice daily, with anti-Xa monitoring
- D. LMWH once or twice daily, without anti-Xa monitoring

## Which anticoagulants can safely be used during pregnancy?

Anticoagulant	Acceptability in Pregnancy	Comments
<b>LMWH</b>	<b>Yes</b>	<ul style="list-style-type: none"> <li>Does not cross the placenta</li> <li>LMWH preferred over UFH due to maternal safety profile (likely lower risk of HIT, reduced bone mineral density)</li> </ul>
<b>UFH</b>	<b>Yes</b>	<ul style="list-style-type: none"> <li>Does not cross the placenta</li> </ul>
<b>Fondaparinux</b>	Not preferred	<ul style="list-style-type: none"> <li>Reported to cross placenta in small amounts</li> <li>Clinical experience with fondaparinux very limited</li> </ul>
<b>Vitamin K Antagonist (VKA)</b>	No	<ul style="list-style-type: none"> <li>Crosses the placenta</li> <li>Potential for teratogenicity, pregnancy loss, fetal bleeding, neurodevelopmental deficits</li> </ul>
<b>Direct Oral Anticoagulants</b>	No	<ul style="list-style-type: none"> <li>Dabigatran and Xa inhibitors likely cross the placenta</li> <li>Reproductive effects in humans are unknown</li> </ul>

## Recommendation

For pregnant women with **acute VTE** treated with LMWH, the panel suggest either once-daily or twice-daily dosing regimens (*conditional recommendation, very low certainty*).

LMWH dosed **twice daily** compared with **once daily**:

Clinical Outcome	Number of Studies	Impact of Dosing Regimens
● Recurrent PE	2 observational studies	Low overall incidence of VTE (<1%), with no difference between two dosing schedules
● Recurrent DVT	2 observational studies	Low overall incidence of VTE (<1%), with no difference between two dosing schedules
● Major Bleeding (antenatal or postpartum)	2 observational studies	Low overall incidence of major bleeding (<1%), with no difference between two dosing schedules

*Low certainty and imprecision in estimates of benefits and harms*  
Therefore either once- or twice-daily dosing appears reasonable. Consider potential impact of dosing frequency on feasibility and acceptability.

## Recommendation

For pregnant women receiving **therapeutic LMWH** for the treatment of VTE, the panel suggests against routine monitoring of anti-Xa levels to guide dosing (*conditional recommendation, low certainty*).

### Remarks:

- Only limited direct data: one small observational study (n = 26) with 11 patients receiving anti-Xa monitoring, 15 receiving no anti-Xa monitoring; no difference in recurrent VTE or bleeding
- **Anti-Xa tests may be unreliable and not routinely available in all centres**
- **No established therapeutic range for LMWH in pregnancy**
- ***Potential drawbacks of testing:*** frequent blood tests, clinic visits, cost

**In absence of evidence of benefit, the panel suggests against routine monitoring anti-Xa during treatment for VTE**



## Does this patient need to be admitted? Not necessarily.

### Recommendation

In pregnant women with low risk acute VTE, the panel suggests initial outpatient therapy over hospital admission (*conditional recommendation, low certainty*).

#### *In non-pregnant patients:*

- Outpatient treatment associated with better patient satisfaction and social functioning without negative impact on VTE outcomes.

#### *Extrapolating from non-pregnant data (and observational data in pregnancy):*

- Outpatient therapy in pregnancy likely as beneficial as hospital-based treatment, with improved acceptability.

#### *Caution: outpatient therapy may not be appropriate for non-low-risk individuals:\*\**

- Abnormal vital signs
- Severe analgesic needs
- Extensive VTE
- Advanced gestational age
- Maternal comorbidities
- Contraindications to LMWH
- Lack of home support

\*\*Outpatient therapy **only appropriate** if patients provided appropriate education, follow-up assured, and on-call services available. If expertise for patient training and outpatient monitoring not available, low-risk patients may benefit from initial hospitalization.





Your patient has a proximal DVT in the common femoral vein. You start her on full dose LMWH, once daily. After 3 days of outpatient treatment she is ambulatory, but continues to complain of swelling and pain in her thigh.

*She asks: “Should we remove the clot more quickly? Will that help me feel better and improve my chances for recovery in future?”*

Should you refer this patient for catheter-directed thrombolysis (CDT)?

A. Yes

B. No



## Recommendation

In pregnant women with **acute lower-extremity deep vein thrombosis**, the panel suggests against the addition of catheter-direct thrombolysis therapy to anticoagulation (*conditional recommendation, low certainty*)

### Remarks:

- In non-pregnant individuals, **CDT does not appear to reduce the risk of post-thrombotic syndrome**, except possibly those with iliofemoral DVT (ATTRACT study)
- Pregnancy-specific data limited to case series with low certainty of evidence, so difficult to draw substantive conclusions regarding benefit
- **Possible harms from CDT:** fetal radiation exposure, increase in major bleeding (ATTRACT study)

At this juncture, CDT is probably best reserved for those with limb-threatening deep vein thrombosis

## Case 1: Continued

- You elect against CDT, and your patient continues on full dose LMWH (dalteparin 200 IU/kg) once daily, without anti-Xa monitoring
- Within 2 weeks, her leg swelling and pain improve substantially
- She is now 35 weeks gestational age and you are evaluating her in your clinic before her delivery date



Your patient is on therapeutic dose LMWH. She is 35 weeks gestational age and her estimated delivery date is 5 weeks from today. She would prefer to have a vaginal delivery with epidural anesthesia.

What do you suggest for managing her anticoagulation around the time of delivery?

- A. Switch anticoagulation to intravenous heparin, then scheduled (induced) delivery with discontinuation of IV heparin 6 hours before
- B. Scheduled (induced) delivery with discontinuation of LMWH 24 hours before
- C. Allow for spontaneous labour before stopping LMWH anticoagulation
- D. Scheduled cesarean section with discontinuation of LMWH 24 hours before
- E. Stop her LMWH now as she no longer requires anticoagulation

## Recommendation

For pregnant women receiving **therapeutic-dose LMWH** for VTE, the panel suggests **scheduled delivery** with prior discontinuation of anticoagulant therapy (*conditional recommendation, very low certainty*)

### Remarks:

- Observational data *suggest increase in postpartum hemorrhage* if therapeutic anticoagulation stopped with spontaneous onset of labor, compared with planned induction (RR 1.9, 95% CI 0.6 to 5.8)
- North American anesthesia guidelines specify **24-hour interval** between therapeutic LMWH and placement of neuraxial anesthesia
- Induction of labor is not associated with maternal or fetal harm

A scheduled induction may facilitate neuraxial anesthesia and reduce maternal bleeding risk (*very low certainty of evidence*)



## Case 1: Continued

- She undergoes a scheduled, induced vaginal delivery at 40 weeks gestational age. Her last dose of LMWH is given 24 before her induction date, and the delivery is uncomplicated
- You are now assessing her in the postpartum setting. Hemostasis has been achieved, and the obstetrics team is comfortable with resumption of full dose anticoagulation
- Your patient plans on breastfeeding her new infant

Your patient requires 6 weeks of postpartum anticoagulation for her pregnancy-associated VTE. She plans on breastfeeding.

Which ONE of the following anticoagulants is contraindicated in breastfeeding women?

- A. Fondaparinux
- B. LMWH
- C. Danaparoid
- D. Rivaroxaban
- E. Warfarin

## Recommendations

- For breastfeeding women who have an indication for anticoagulation, the panel recommends using **UFH, LMWH, warfarin, acenocoumarol, fondaparinux, or danaparoid as safe options** (*strong recommendation, low certainty*)
- For breastfeeding women who have an indication for anticoagulation, the panel recommends **against using direct-acting oral anticoagulants** (*strong recommendation, very low certainty*)

Anticoagulant	Acceptability in Breastfeeding	Comments
<b>UFH</b>	<b>Yes</b>	<ul style="list-style-type: none"> <li>• Does not pass into breast milk due to large size and negative charge</li> </ul>
<b>LMWH</b>	<b>Yes</b>	<ul style="list-style-type: none"> <li>• Excreted into breast milk in small amounts, but limited bioavailability so unlikely to be absorbed by newborn</li> </ul>
<b>Non-lipophilic VKA</b>	<b>Yes</b>	<ul style="list-style-type: none"> <li>• Non-lipophilic VKAs (<b>warfarin, acenocoumarol</b>) unlikely to be secreted in breast milk; small studies showing no detectable levels</li> </ul>
<b>Rivaroxaban</b>	No	<ul style="list-style-type: none"> <li>• Case reports suggesting low excretion of rivaroxaban into breast milk (estimated relative infant dose &lt; 2%), but limited experience</li> <li>• <b><i>Paucity of data on all direct oral anticoagulants, including rivaroxaban</i></b></li> </ul>





Your patient continues full dose LMWH for an additional 6 weeks. She completes this period of postpartum anticoagulation with no complications.

Three years later, she informs you that she is 10 weeks pregnant with her second child. She is concerned about developing VTE again during pregnancy.

What would you recommend for prevention of VTE during this pregnancy?

- A. No prophylactic anticoagulation is recommended
- B. Serial bilateral leg ultrasound, and treatment only if recurrent DVT is diagnosed
- C. Antepartum anticoagulant prophylaxis only
- D. Postpartum anticoagulant prophylaxis only
- E. Antepartum and postpartum anticoagulant prophylaxis

## Recommendation

For women not already receiving long-term anticoagulant therapy who have a history of VTE, the panel makes the following recommendations:

Prior VTE History	Antepartum Prophylaxis	Postpartum Prophylaxis
<b>Unprovoked VTE</b> <i>(strong recommendation, low certainty)</i>	Yes	Yes
<b>Provoked VTE, Hormonal risk factor</b> <i>(strong recommendation, low certainty)</i>	Yes	Yes
<b>Provoked VTE, Non-Hormonal risk factor</b> <i>(conditional recommendation, low certainty)</i>	No**	Yes

These recommendations were made based on a VTE risk threshold of 2% antepartum and 1% postpartum for recommending LMWH prophylaxis

\*\*as long as no current additional risk factors for VTE



## Antepartum prophylaxis compared with **no antepartum prophylaxis** in pregnant women with prior VTE:

Outcomes	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with no antepartum prophylaxis	Risk difference with antepartum prophylaxis
● Recurrent VTE	<b>RR 0.39</b> (0.21 to 0.72)	27 out of 645 (4.2%)	<b>26 fewer VTE per 1,000</b> (12 fewer to 33 fewer)
● Major bleeding, antepartum	<b>RR 0.34</b> (0.04 to 3.21)	3 out of 473 (0.6%)	<b>4 fewer bleeds per 1,000</b> (6 fewer to 14 more)
● Major bleeding, peripartum	<b>RR 0.82</b> (0.36 to 1.86)	12 out of 395 (3.0%)	<b>5 fewer bleeds per 1,000</b> (19 fewer to 26 more)

In pooled estimates, in the antepartum period the risks of recurrent VTE are:

- **Without** antepartum prophylaxis: **4.2%** (95% CI, 0.3% to 6.0%)
- **With** antepartum prophylaxis provided: **0.9%** (95% CI, 0.5% to 1.8%)

**Postpartum prophylaxis** compared with **no postpartum prophylaxis** in pregnant women with prior VTE:

Outcomes	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with no postpartum prophylaxis	Risk difference with postpartum prophylaxis
● Recurrent VTE	<b>RR 0.27</b> (0.15 to 0.49)	22 out of 337 (6.5%)	<b>48 fewer VTE per 1,000</b> (33 fewer to 55 fewer)
● Major bleeding, postpartum	<b>RR 0.71</b> (0.03 to 14.70)	3 out of 473 (0.6%)	<b>0 fewer bleeds per 1,000</b> (0 fewer to 0 fewer)
● Major bleeding, peripartum	<b>RR 0.82</b> (0.36 to 1.86)	12 out of 395 (3.0%)	<b>5 fewer bleeds per 1,000</b> (19 fewer to 26 more)

In pooled estimates, in the postpartum period the risks of recurrent VTE are:

- **Without** antepartum prophylaxis: **6.5%** (95% CI, 4.3% to 9.7%)
- **With** antepartum prophylaxis provided: **1.8%** (95% CI, 1.2% to 2.7%)



## Case 1: Conclusion

- After careful consideration, your patient is started on **antepartum and postpartum anticoagulant prophylaxis** with prophylactic LMWH
- The pregnancy proceeds without signs or symptoms of VTE recurrence



## Case 1: Summary

LMWH dosed either once or twice daily, without routine anti-Xa monitoring, is the preferred treatment for acute VTE in pregnancy

Pregnant women who are receiving therapeutic LMWH for pregnancy-associated VTE should have a scheduled delivery to facilitate neuraxial anesthesia and reduce bleeding risk

Women with previous unprovoked VTE or VTE provoked by hormonal risk factors should receive antepartum and postpartum anticoagulant prophylaxis

## Case 2: Deciding About Prophylaxis

32 year old female, 12 weeks gestational age, 1<sup>st</sup> pregnancy

**Past Medical History:** None.

**Medications:** Prenatal Vitamin

**You are assessing her in your clinic:**

- She has no personal history of arterial or venous thrombosis
- There is a positive family history for VTE
  - Mother: postpartum PE at age 32
  - Mother's sister: unprovoked DVT at age 34

Both family members have been diagnosed with **Antithrombin Deficiency**; mother's Antithrombin activity was 0.35 U/mL (normal > 0.80 U/mL)



Your patient has no personal history of VTE. There is a significant family history of VTE, and confirmed Antithrombin Deficiency. You arrange for testing, and your patient is found to have an Antithrombin activity of 0.38 U/mL (normal > 0.80).

What would you suggest for prevention of pregnancy-associated VTE during her first pregnancy?

- A. No prophylactic anticoagulation is recommended
- B. Serial bilateral leg ultrasound and treatment only if recurrent DVT is diagnosed
- C. Antepartum anticoagulant prophylaxis only
- D. Postpartum anticoagulant prophylaxis only
- E. Antepartum and postpartum anticoagulant prophylaxis



## Recommendation

For women who **do not** have a personal history of VTE, the panel recommends:

Hereditary Thrombophilia in Patient	Family History of VTE	Antepartum Prophylaxis	Postpartum Prophylaxis
Heterozygous PGM <i>or</i> Heterozygous Factor V Leiden	(+)	● No	● No
	(-)	● No	● No
Protein S Deficiency <i>or</i> Protein C Deficiency	(+)	● No	● Yes
	(-)	● No	● No
Antithrombin Deficiency	(+)	● Yes	● Yes
	(-)	● No	● No

These recommendations were made based on a VTE risk threshold of **2% antepartum** and **1% postpartum** for recommending LMWH prophylaxis

**Our patient:**  
*Antithrombin deficiency with (+) family history.*  
Her estimated risk of VTE is 2.7% antepartum, 4.8% postpartum which exceed risk thresholds for prophylaxis.

## Recommendation

For women who **do not** have a personal history of VTE, the panel recommends:

Hereditary Thrombophilia in Patient	Family History of VTE	Antepartum Prophylaxis	Postpartum Prophylaxis
Homozygous PGM	(+)	● No formal recommendation**	● Yes
	(-)	● No	● Yes
Homozygous Factor V Leiden	(+)	● Yes	● Yes
	(-)	● Yes	● Yes
Combined thrombophilia	(+)	● Yes	● Yes
	(-)	● Yes	● Yes

\*\*No formal recommendation as no family studies available in homozygous PGM. However, panel members favor antepartum prophylaxis given VTE risk estimates

Your patient requires antepartum and postpartum anticoagulant prophylaxis.

What dose of prophylactic LMWH is suggested for patients requiring antepartum and postpartum prophylaxis?

- A. Antepartum: standard dose, Postpartum: standard dose
- B. Antepartum: standard dose, Postpartum: intermediate dose
- C. Antepartum: intermediate dose, Postpartum: intermediate dose
- D. Antepartum: intermediate dose, Postpartum: therapeutic dose

## Recommendation

- For pregnant women who require prophylaxis, the panel suggests against intermediate-dose LMWH prophylaxis compared to standard-dose LMWH prophylaxis during the **antepartum period** (*conditional recommendation, very low certainty*)
- The panel suggests either standard- or intermediate-dose LMWH prophylaxis during the **postpartum period** (*conditional recommendation, very low certainty*)

### Remarks:

- *Very low certainty evidence suggesting unclear net health benefit for using intermediate dosing*
- However, difficult to make significant conclusions given limitations in evidence

- Favor standard-dose antepartum to minimize risks of bleeding or delayed epidural access
- Standard- or intermediate-dose reasonable for postpartum prophylaxis given increased thrombotic risk after delivery

## Case 2: Continued

- After discussing the benefits and risks, you start your patient on antepartum and postpartum anticoagulant prophylaxis with prophylactic LMWH.
- She tolerates the injections, and there are no signs or symptoms of VTE. She develops no bleeding or bruising.
- You are now seeing her in your clinic at 35 weeks gestational age.



She is 35 weeks gestational age and will be delivering at 40 weeks, she hopes via vaginal delivery with epidural anesthesia.

What would you suggest for management of her prophylactic LMWH around delivery?

- A. Switch anticoagulation to intravenous heparin, then scheduled (induced) delivery with discontinuation of IV heparin 6 hours before
- B. Scheduled (induced) delivery with discontinuation of LMWH 24 hours before
- C. Allow for spontaneous labor before stopping LMWH anticoagulation
- D. Scheduled cesarean section with discontinuation of LMWH 24 hours before
- E. Stop her LMWH now as she no longer requires anticoagulation for her DVT

## Recommendation

In pregnant women receiving **prophylactic-dose LMWH**, the panel suggests against scheduled delivery with discontinuation of prophylactic anticoagulation compared to allowing spontaneous labor (*conditional recommendation, very low certainty*)

### Remarks:

- No clear evidence of increased bleeding risk with spontaneous delivery on prophylactic LMWH
- Allowing spontaneous labor may minimize the need for medical intervention in labor, and **reduce the medicalization of delivery** that may occur with induction of labor
- North American anesthetic guidelines call for **12-hour interval** between last prophylactic dose of LMWH and epidural catheter placement

12-hour interval between last dose of standard prophylactic LMWH and epidural catheter would allow most women to receive neuraxial anesthesia regardless of scheduled or spontaneous delivery

However, women or healthcare providers who place a high priority on access to epidural anesthesia **may prefer a scheduled delivery**

## Case 2: Conclusion

- She continues prophylactic LMWH, and opts for spontaneous labor instead of a scheduled (induced) delivery
- At 39 weeks gestational age, she presents to the hospital with regular contractions. She stops her prophylactic LMWH at that point
- 14 hours later she is progressing in labor and an epidural catheter is inserted. The labor is uneventful, and prophylactic LMWH is resumed postpartum when hemostasis is achieved





## Case 2: Summary

Pregnant women with no personal history of VTE may merit anticoagulant prophylaxis depending on their family history of VTE and whether there is underlying thrombophilia

Pregnant women who are receiving prophylactic-dose LMWH do not necessarily require scheduled (induced) delivery

## Case 3: Superficial Vein Thrombosis

32 year old female, 26 weeks gestational age, 1<sup>st</sup> pregnancy

**Past Medical History:** Bilateral varicose veins

**Medications:** Prenatal vitamin

**You are assessing her in your clinic:**

- 48 hours of tender, indurated varicose veins along her right calf, popliteal fossa, and medial thigh

**Bilateral compression ultrasounds of the lower extremities:**

- No evidence of proximal DVT
- 8 cm greater saphenous vein thrombosis (superficial vein thrombosis) extending from calf to mid-thigh



She has no evidence of DVT, but has symptomatic thrombus in her greater saphenous vein.

What would you suggest for management of her superficial vein thrombosis?

- A. Warm compresses and non-steroidal anti-inflammatory medications (no anticoagulants)
- B. Fondaparinux
- C. LMWH
- D. Graduated compression stockings

## Recommendation

For pregnant women with proven **acute superficial vein thrombosis**, the panel suggests that **LMWH be used over not using any anticoagulant** (*conditional recommendation, low certainty*)

**Anticoagulant** vs. **no anticoagulant** for acute superficial vein thrombosis in pregnancy (data from non-pregnant studies):

Outcomes	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with no anticoagulation	Risk difference with anticoagulation
● Any symptomatic VTE	<b>RR 0.15</b> (0.04 to 0.50)	20 out of 1500 (1.3%)	<b>11 fewer VTE per 1,000</b> (7 fewer to 13 fewer)
● Extension to SFJ	<b>RR 0.08</b> (0.03 to 0.22)	51 out of 1500 (0.6%)	<b>31 fewer ext. per 1,000</b> (27 fewer to 33 fewer)
● Major bleeding	<b>RR 0.99</b> (0.06 to 15.90)	1 out of 1488 (0.1%)	<b>0 fewer bleeds per 1,000</b> (1 fewer to 10 more)

**No specific data in pregnancy.**

*Anticoagulants likely reduce risk of VTE from SVT.*

Fondaparinux crosses the placenta, so LMWH preferred.



## Case 3: Conclusion and Summary

- She starts LMWH at a prophylactic dose and continues this anticoagulant throughout the remainder of her pregnancy
- Within 1 week her symptoms substantially improve and there are no symptoms of proximal extension or PE
- She continues the prophylactic LMWH until 6 weeks postpartum

It is likely that anticoagulants reduce the risk of VTE after SVT, with LMWH preferred for treatment of SVT in pregnancy.

## Other guideline recommendations that were not covered in this session

*For these topics, conditional recommendations were made based on weak or very weak quality of evidence*

- Anticoagulant prophylaxis for assisted reproductive technologies
- Anticoagulant prophylaxis for ovarian hyperstimulation syndrome
- Role of systemic thrombolysis for acute PE in pregnancy
- Diagnosis of suspected pulmonary embolism in pregnancy

## Future Priorities for Research

- Safety of fondaparinux and direct oral anticoagulants in pregnancy
- Evidence regarding once versus twice daily dosing of LMWH
- Data regarding efficacy of catheter-directed thrombolysis, including estimated fetal radiation exposure
- Safety of direct oral anticoagulants in breastfeeding women
- Data regarding intensity of LMWH prophylaxis
- Data regarding impact of thrombophilia on antepartum VTE risk
- Validation of clinical prediction rules for diagnosis of VTE

## In Summary: Back to our Objectives

1. Describe recommendations for the management of acute VTE in pregnancy
  - LMWH, once or twice daily, without routine anti-Xa monitoring
2. Describe which anticoagulants can safely be used in women who are pregnant or breastfeeding
  - **Pregnancy:** LMWH or UFH; **Breastfeeding:** LMWH, UFH, warfarin, acenocoumarol, fondaparinux, danaparoid
3. Identify which pregnant patients merit antepartum and/or postpartum VTE prophylaxis
  - All patients with prior VTE merit **postpartum prophylaxis**
  - Prior unprovoked and hormonal provoked VTE merit **antepartum prophylaxis**
  - For women with thrombophilias, recommendations vary according to thrombophilia and family history





## Acknowledgements

- ASH Guideline Panel team members
- Knowledge Synthesis team members
- McMaster University GRADE Centre
- Author of ASH VTE Slide Sets: **Eric Tseng MD MScCH, University of Toronto** and **Shannon Bates MDCM MSc, McMaster University**

See more about the **ASH VTE guidelines** at <http://www.hematology.org/VTEguidelines>