Prevention of VTE in pregnancy

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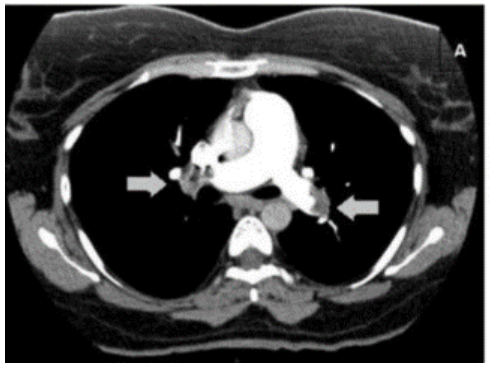
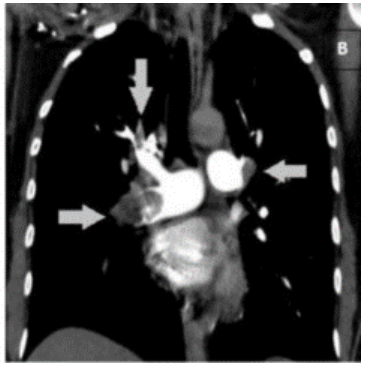




June 11, 2020

Thrombosis UK Webinar

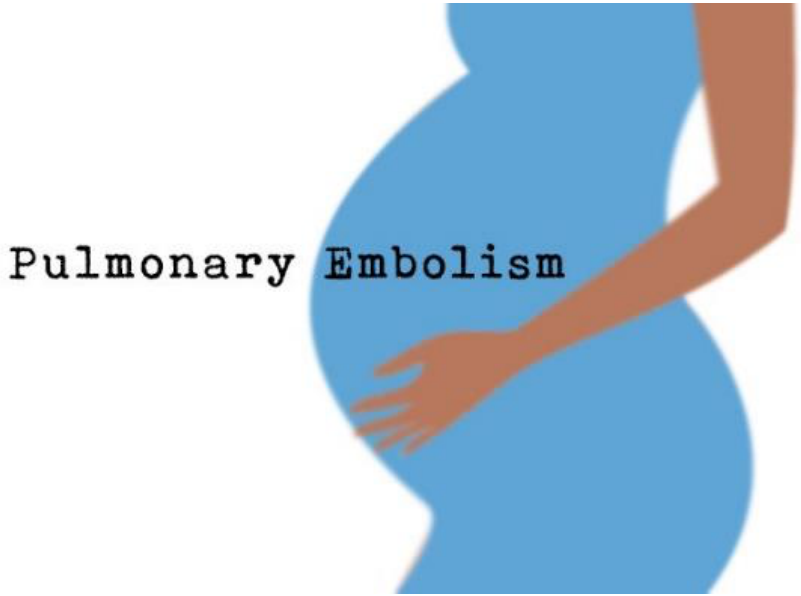
Conflict Of Interest Disclosure

❑ **I have the following real or perceived conflicts of interest that relate to this presentation:**

Affiliation / Financial interest	Commercial Company
Grants/research support:	Aspen; Bayer; Boehringer Ingelheim; Daiichi Sankyo
Honoraria or consultation fees:	Aspen; Bayer; BMS/Pfizer; Boehringer Ingelheim; Portola; Sanofi
Participation in a company sponsored bureau:	n.a.
Stock shareholder:	n.a.
Spouse / partner:	n.a.
Other support / potential conflict of interest:	n.a.

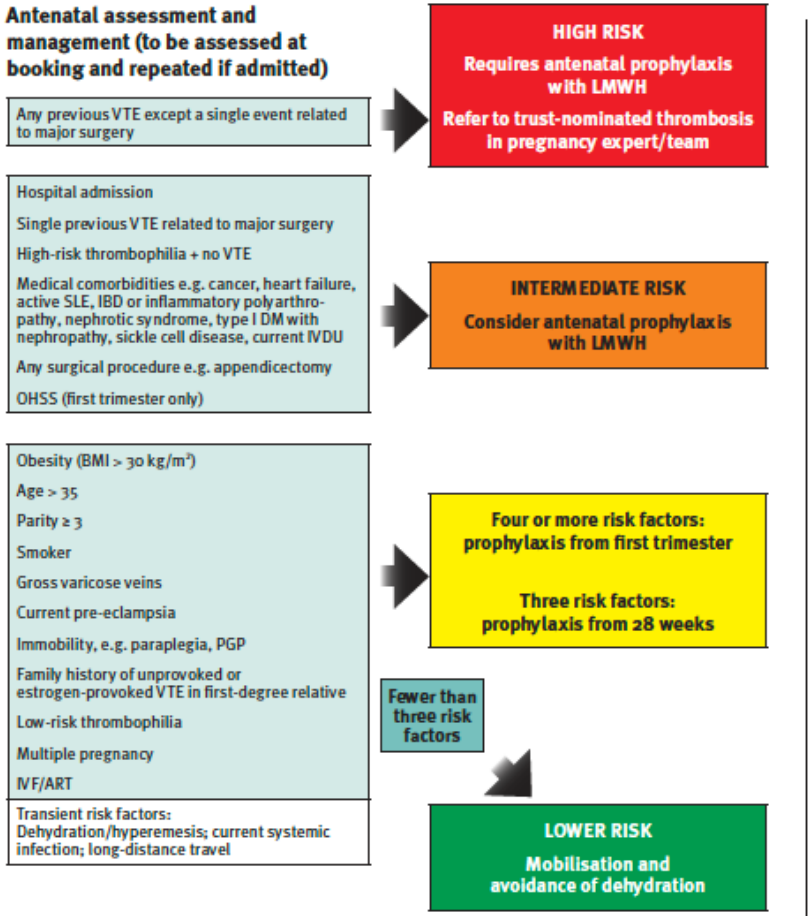
All fees are transferred to my institution

Leading Cause of Maternal Death in Western World:



Bourjeily, Lancet 2010, Greer NEJM 2015, Heit Ann Intern Med 2005, James Am J Obstet Gynecol 2006

Appendix I: Obstetric thromboprophylaxis risk assessment and management



Here we go with some cases

1. 39 years old
2. BMI 31
3. Pregnant after ART
4. Goes visit her family in the US

Or

1. 36 years old
2. Pregnant with twins
3. Hyperemesis
4. Family history of VTE
5. Factor V Leiden

RCOG 2015

Marked differences between guidelines

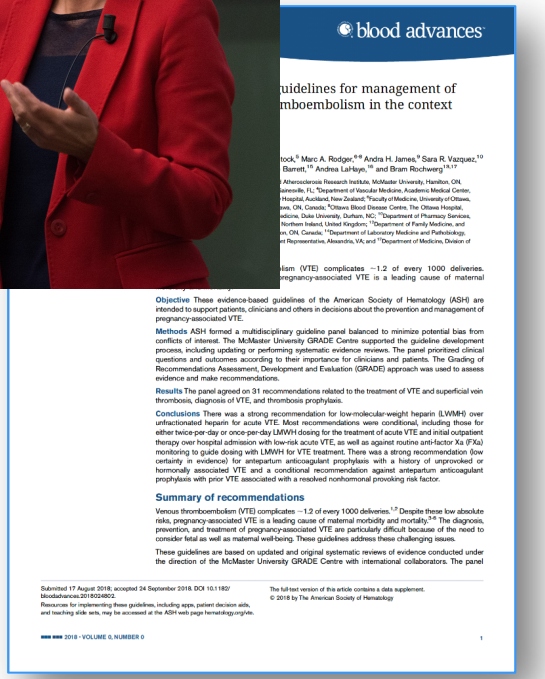
Table 3. Guideline summary: prevention of first VTE in pregnant women with hereditary thrombophilia

American Society of Hematology (ASH)	Society of Obstetricians and Gynecologists of Canada (SOGC)*,[235]	Royal College of Obstetricians and Gynecologists (RCOG)†,[240]	American College of Obstetricians and Gynecologists (ACOG)‡,[239]	American College of Chest Physicians (ACCP)§,[237]
Heterozygosity for factor V Leiden or prothrombin gene mutation				
Antepartum: Regardless of family history of VTE, the ASH guideline panel *suggests against* using antepartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects).	Antepartum: Clinical surveillance (no grade).	Antepartum: Clinical surveillance unless additional risk factors are present; with a weighted score of at least 3,‖ thrombosis prophylaxis throughout the antepartum period should be considered; if the weighted score is only 2,‖ prophylaxis should be considered from 28 weeks (D).	Antepartum: Either clinical surveillance or prophylactic LMWH or UFH (no grade).	Antepartum: For pregnant women who are heterozygous for factor V Leiden mutation or prothrombin gene mutation, suggest antepartum clinical surveillance (regardless of family history of VTE) (grade 2C).
Postpartum: For women without a family history of VTE, the ASH guideline panel *suggests against* antithrombotic prophylaxis in the postpartum period to prevent a VTE (conditional recommendation, very low certainty in evidence about effects). For women with a family history of VTE, the ASH guideline panel *suggests against* postpartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects).	Postpartum: Clinical surveillance or prophylaxis if present in combination with any 2 of the following risk factors (each with an absolute risk of VTE <1% in isolation): BMI ≥30 kg/m^2 at first antepartum visit (II-2B), smoking >10 cigarettes per day antepartum (II-2B), preeclampsia (II-2B), intrauterine growth restriction (II-2B), placenta previa (II-2B), emergency cesarean section (II-2B), peripartum or postpartum blood loss of >1 L or need for blood product replacement (II-2B), preterm delivery (III-B), stillbirth (III-B), or maternal disease (cardiac disease, systemic lupus erythematosus, sickle cell disease, inflammatory disease, varicose veins, gestational diabetes) (III-B). If prescribed, prophylaxis should be given for 6 weeks (II-3B).	Postpartum: Consider thromboesis prophylaxis for at least 10 days after delivery if additional risk factors are present with a weighted score of at least 1‖; if there is a family history of VTE in a first-degree relative, thrombosis prophylaxis should be extended to 6 weeks (D).	Postpartum: Either clinical surveillance or anticoagulation if there are additional risk factors (first-degree relative with thrombotic episode before age 50 years or other major thrombotic risk factor (eg, obesity, prolonged immobility) (no grade).	Postpartum: For pregnant women who are heterozygous for factor V Leiden or prothrombin gene mutation, suggest postpartum clinical surveillance if there is no family history of VTE and postpartum prophylaxis with prophylactic- or intermediate-dose LMWH, or vitamin K antagonists targeted at an INR of 2.0 to 3.0 for 6 weeks if there is a family history of VTE rather than routine care (grade 2C).
Protein C deficiency				
Antepartum: Regardless of family history of VTE, the ASH guideline panel *suggests against* using antepartum antithrombotic prophylaxis to prevent a first VTE (conditional recommendation, very low certainty in evidence about effects).	Antepartum: Clinical surveillance (no grade).	Antepartum: Advice of a local expert should be sought and antepartum LMWH should be considered (D).	Antepartum: Either clinical surveillance or prophylactic LMWH or UFH (no grade).	Antepartum: For pregnant women who are protein C deficient, suggest antepartum clinical surveillance (regardless of family history of VTE) (grade 2C).

Bates et al, ASH guideline 2018

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



blood advances

uidelines for management of
mboembolism in the context

tock,[9] Marc A. Rodger,[9-11] Andra H. James,[9] Sara R. Vazquez,[10]
Barrett,[15] Andrea LaHaye,[16] and Bram Rochwerg[16,17]

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edicine, Duke University, Durham, NC; [10]Department of Pharmacy Services,
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ism (VTE) complicates ~1.2 of every 1000 deliveries.
regnancy-associated VTE is a leading cause of maternal

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 (LWMH) 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.[1,2] Despite these low absolute risks, pregnancy-associated VTE is a leading cause of maternal morbidity and mortality.[3-8] 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

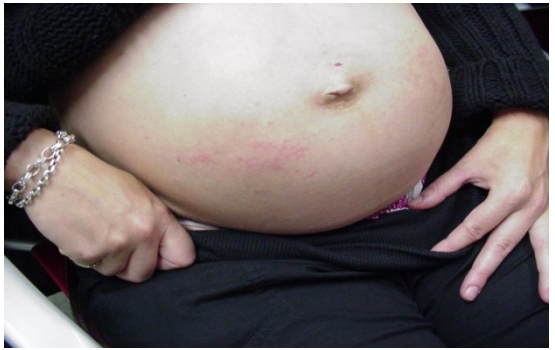
Submitted 17 August 2018; accepted 24 September 2018. DOI 10.1182/bloodadvances.2018024802.
Resources for implementing these guidelines, including apps, patient decision aids, and teaching slide sets, may be accessed at the ASH web page hematology.org/vte.

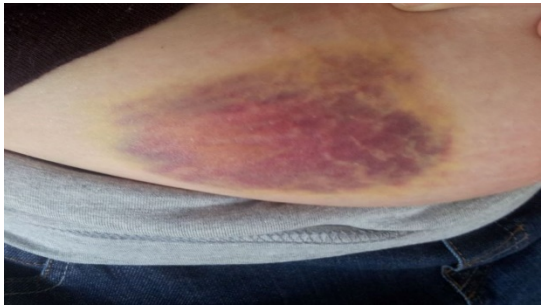
The full-text version of this article contains a data supplement.

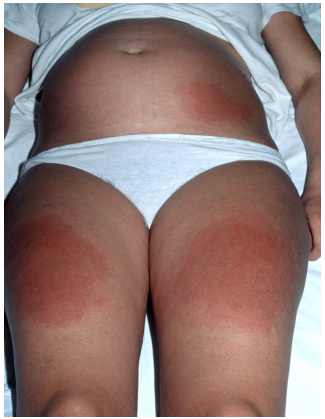
Are we doing too much? side effects of LMWH

- **Daily injections**
- **Skin reactions**
  - 20-40% of women, type IV delayed type hypersensitivity
  - Bleeding
  - Around delivery
- **Caveat epidurals**

- **HIT (<0.1%)**
- **Osteoporosis (?)**







LMWH, low molecular weight heparin; HIT, Heparin induced thrombocytopenia
Bank, Thromb Res 2004, Schindewolf J Allergy Clin Immunol 2013, Schultinge Neth J Med 2013

How to strike the right balance?

It is all about absolute risks of benefits vs harms

It is all about absolute risks of benefits vs harms

Believe it or not, BUT

- **We have NO trial evidence on the efficacy of VTE prophylaxis in pregnancy or postpartum period**

- **We only have bleeding data from**
  - cohort studies
  - LMWH trials not designed to collect bleeding
  - Massive underreporting

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
Unprovoked VTE *(strong recommendation, low certainty)*	Yes	Yes
Provoked VTE, Hormonal risk factor *(strong recommendation, low certainty)*	Yes	Yes
Provoked VTE, Non-Hormonal risk factor *(conditional recommendation, low certainty)*	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	**RR 0.39** (0.21 to 0.72)	27 out of 645 (4.2%)	**26 fewer VTE per 1,000** (12 fewer to 33 fewer)
Major bleeding, antepartum	**RR 0.34** (0.04 to 3.21)	3 out of 473 (0.6%)	**4 fewer bleeds per 1,000** (6 fewer to 14 more)
Major bleeding, peripartum	**RR 0.82** (0.36 to 1.86)	12 out of 395 (3.0%)	**5 fewer bleeds per 1,000** (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%)

Quality of Evidence (GRADE): Low Moderate Strong

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	**RR 0.27** (0.15 to 0.49)	22 out of 337 (6.5%)	**48 fewer VTE per 1,000** (33 fewer to 55 fewer)
Major bleeding, postpartum	**RR 0.71** (0.03 to 14.70)	3 out of 473 (0.6%)	**0 fewer bleeds per 1,000** (0 fewer to 0 fewer)
Major bleeding, peripartum	**RR 0.82** (0.36 to 1.86)	12 out of 395 (3.0%)	**5 fewer bleeds per 1,000** (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%)

Quality of Evidence (GRADE): Low Moderate Strong

How To Deal With Thrombophilia

Recommendation

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

Presentation	Family History of VTE	Antepartum Prophylaxis	Postpartum Prophylaxis
Heterozygous for factor V Leiden mutation	Yes	No ●	No ●
	No	No ●	No ●
Homozygous for factor V Leiden mutation	Yes	Yes ●	Yes ●
	No	Yes ●	Yes ●
Heterozygous for prothrombin mutation	Yes	No ●	No ●
	No	No ●	No ●
Homozygous for prothrombin mutation	Yes	Yes[1] ●	Yes ●
	No	No ●	Yes ●
Protein C deficiency	Yes	No ●	Yes ●
	No	No ●	No ●
Protein S deficiency	Yes	No ●	Yes ●
	No	No ●	No ●
Antithrombin deficiency	Yes	Yes ●	Yes ●
	No	No ●	No ●
Combined thrombophilias	Yes	Yes ●	Yes ●
	No	Yes ●	Yes ●

● = Strong Recommendation ● = Conditional Recommendation

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

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

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

T HIGH LOW nderway

Objective

- Efficacy and safety of intermediate dose LMWH versus low dose LMWH in pregnant women with a history of VTE

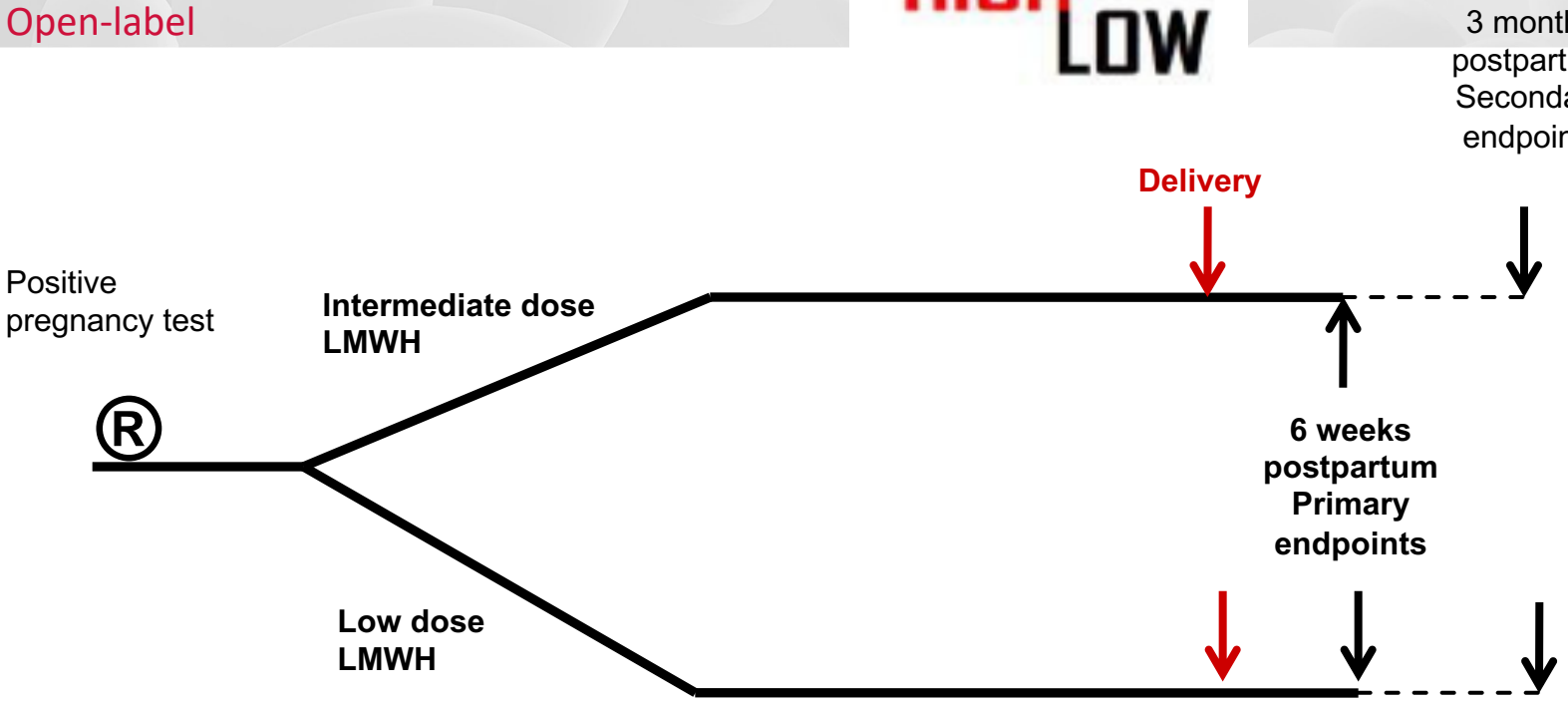
Hypothesis

- Intermediate dose LMWH is superior in preventing recurrent VTE to low dose LMWH, with an acceptable safety profile

Study Design

Open-label

HIGH LOW



9 countries, > 70 sites, > 1030 patients randomised (June 2020)

www.highlowstudy.org

www.clinicaltrials.gov 01828697

Conclusions

- Most women with a history of prior VTE should receive antepartum and postpartum LMWH prophylaxis
- Pregnant women with no personal history of VTE may merit LMWH prophylaxis depending on their family history of VTE and whether there is underlying thrombophilia
- The optimal prophylactic dose is unknown, but evidence is underway (Q1, 2022)

Our Patients Deserve Trials and High-Quality Evidence

- Investigate
- Collaborate
- Identify
- Improve