The Risk of Bleeding in Pregnant Women with Acute Venous Thromboembolism Treated with Anticoagulants

Camille Simard, MD

Department of Epidemiology, Biostatistics and Occupational Health

McGill University, Montreal

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ABSTRACT

Women are at an increased risk of venous thromboembolism (VTE) during pregnancy and the postpartum period. VTE complicates 1 to 2 of 1000 pregnancies and is an important cause of maternal morbidity and mortality. During pregnancy, subcutaneous weight-adjusted low-molecular-weight-heparin (LMWH) is the standard anticoagulation therapy for acute VTE. Women receive a minimum of three months of LMWH with treatment generally extended throughout pregnancy and for at least six weeks following delivery. Heterogeneous estimates are reported in the literature pertaining to the risk of bleeding among patients treated with therapeutic-dose anticoagulation. Most studies reporting bleeding among patients on LMWH during pregnancy combine various doses and indications for LMWH. Individual LMWHs, including dalteparin, enoxaparin and tinzaparin, are considered as having similar anticoagulant properties. However, they differ in their pharmacodynamic and pharmacokinetic properties, which may impact anticoagulant-related bleeding. Moreover, Canadian utilization data for LMWHs in the general population have shown that over 50% of prescriptions dispensed are for dalteparin. Since dalteparin is the preferred LMWH, determining whether it confers a benefit regarding bleeding complications is important.

In the first study, we systematically reviewed the literature to identify studies evaluating bleeding complications among patients treated with therapeutic-dose LMWH for the treatment of VTE during pregnancy and highlight the limitations of the existing literature. Five observational studies were included, all of which were deemed to have a serious to critical risk of bias using the ROBINS-I tool. The percentage of bleeding in these studies ranged between 2.9% and

30.0%. The ability to draw definitive conclusions is limited by the low quality of the existing literature, as well as the heterogeneity of bleeding definitions used.

In the second study, we conducted a population-based cohort study using data from electronic healthcare databases from the province of Québec to examine the relationship between the use of different therapeutic LMWHs and the risk of bleeding among pregnant women. The objectives were to compare bleeding incidence between the most commonly used LMWH, dalteparin, vs. enoxaparin or tinzaparin, compare bleeding estimates between these groups with regards to antepartum and postpartum bleeding, and compare bleeding in patients receiving once vs. twice daily dosing of any LMWH. We included women with a diagnosis of VTE during pregnancy, a prescription for LMWH and a defined bleeding event using inpatient diagnostic codes for bleeding, including pregnancy-related and non-pregnancy related bleeding. A total of 259 pregnant women with VTE were included. Overall, 20 patients (7.7%) had a hospitalization with bleeding and the incidence rate of bleeding was 310.5 per 1000 person-years. Conclusions regarding a potential difference in the risk of bleeding between dalteparin and enoxaparin or tinzaparin were limited by the uncertainty around the estimates; however, the risk estimate was close to the null (hazard ratio (HR) 0.9, 95% confidence interval (CI) 0.2-2.5). A similar pattern was observed when comparing treatment with once vs. twice daily LMWH (HR 0.8, 95% CI 0.2-2.9). Sensitivity analyses performed were consistent with the main findings.

We provide an overview of knowledge to date on bleeding in women treated for a VTE during pregnancy and provide a population-based estimate of antepartum and postpartum bleeding in patients receiving therapeutic-dose LMWH for VTE during pregnancy. We show that

dalteparin does not appear to have a favourable safety profile compared to enoxaparin or tinzaparin with regards to bleeding complications. Our conclusions are limited by the imprecision around the reported bleeding estimates. Further studies including standardized bleeding definitions are needed to optimize the care of this patient population.

ABBRÉGÉ

Le risque de thromboembolie veineuse (TEV) est augmenté pendant la grossesse et le post-partum. La TEV complique 1 à 2 grossesses sur 1000 et est un cause importante de morbidité et de mortalité maternelles. En grossesse, l'héparine de bas poids moléculaire (HBPM) sous-cutanée ajustée au poids est le traitement recommandé pour la TEV aigüe. Les femmes reçoivent un minimum de trois mois d'HBPM, le traitement étant généralement prolongé jusqu'au moins 6 semaines post-partum. Le risque de saignemement chez les patientes traitées avec HBPM à dose thérapeutique rapporté dans la littérature est variable. Les études décrivent les saignements chez les patientes anticoagulées pendant la grossesse combinant des doses et indications d'HBPM différentes. Les différentes molécules d'HBPM, dont la daltéparine, l'énoxaparine et la tinzaparine, sont considérées comme ayant des propriétés anticoagulantes similaires. Cependant, leurs propriétés pharmacodynamiques et pharmacocinétiques différentes pourraient avoir un impact sur le risque hémorragique. Des données canadiennes sur l'utilisation des HBPM dans la population générale démontrent que plus de 50 % des ordonnances délivrées sont pour la daltéparine. Comme la daltéparine est l'HBPM la plus utilisée, il est important de déterminer si elle confère un avantage quant aux complications hémorragiques.

Dans la première étude, nous avons procédé à une revue systématique de la littérature afin d'identifier les études portant sur les complications hémorragiques des patientes traitées avec une dose thérapeutique d'HBPM pour le traitement de la TEV pendant la grossesse. Cinq études observationelles ont été incluses et ont toutes été jugées comme présentant un risque de biais important à critique en utilisant l'outil ROBINS-I. Le pourcentage de saignements dans ces

études varie entre 2,9 % et 30,0 %. La capacité de tirer des conclusions définitives est limitée par la faible qualité de la littérature existante.

Dans la deuxième étude, nous avons mené une étude de cohorte populationnelle en utilisant une base de données électronique sur les soins de santé de la province de Québec. Les objectifs étaient de comparer l'incidence de complications hémorragiques entre l'HBPM la plus couramment utilisée, la daltéparine, et l'énoxaparine ou la tinzaparine, de comparer les complications hémorragiques entre ces groupes incluant les hémorragies ante-partum et post-partum, et de comparer les complications hémorragiques chez les patientes recevant une dose unique ou deux doses quotidiennes de toute HBPM. Les femmes avec TEV en grossesse et une prescription d'HBPM ont été incluses dans l'étude. Nous avons défini la complication hémorragique en utilisant les codes de diagnostic de complications hémorragiques. Au total, 259 femmes enceintes avec un diagnostic de TEV en grossesse ont été incluses. Vingt patientes (7,7 %) ont été hospitalisées pour une complication hémorragique et le taux d'incidence de complications hémorragiques était de 310,5 pour 1000 personnes-années. Les conclusions concernant une différence potentielle du risque de complication hémorragique entre les deux groupes sont limitées par l'incertitude entourant les estimations ; toutefois, l'estimation du risque était proche de la valeur nulle (hazard ratio (HR) 0,9, intervalle de confiance (IC) à 95 % 0,2-2,5). Les analyses de sensibilité effectuées étaient cohérentes avec les résultats principaux.

Nous fournissons un aperçu des connaissances sur les complications hémorragiques chez les femmes traitées pour TEV pendant la grossesse et fournissons une incidence basée sur des données populationnelles des complications hémorragiques chez ces patientes. La daltéparine ne

semble pas avoir un profil de sécurité favorable par rapport aux autres HBPM pour les complications hémorragiques. Nos conclusions sont limitées par l'imprécision des résultats. Des études futures utilisant une définition standardisée de saignement sont nécessaires.

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Please note that I have received no paid or unpaid assistance by fellow students, research assistants, technicians, or others in the creation of this work.

PREFACE & CONTRIBUTION OF AUTHORS

This thesis is a manuscript-based thesis with six chapters, two of which include manuscripts describing two distinct studies. The first chapter contains the rationale for the thesis and the background to the two studies, as well as a review of the existing literature on the topic. The second chapter includes the manuscript to the study titled, "Bleeding Complications in Women with Venous Thromboembolism during Pregnancy: A Systematic Review of the Literature" and its preface. This work has been published in the Research and Practice in Thrombosis and Haemostasis journal. The third chapter highlights the knowledge gap identified in the systematic review of the literature, highlights current practice variation in the management of anticoagulation in this patient population, as well as the need for population-derived bleeding estimates. The fourth chapter contains the second manuscript titled: "The Risk of Bleeding in Pregnant Women with Acute Venous Thromboembolism Treated with Anticoagulants", as well as supplementary material to the cohort study manuscript including the algorithm used to create the study cohort. The fifth chapter includes a discussion of the overall findings of the thesis, discusses strengths and limitations as well as future next steps. The sixth and final chapter of the thesis incudes the final conclusions of the thesis.

Camille Simard, MD, M.Sc. candidate

I am first author of both manuscripts. For both studies, I developed the study protocols, applied to the Research Review Office for the Centre intégré universitaire de santé et de services sociaux (CIUSSS) of the Centre-Ouest-de-l'Île-de-Montréal via the Research Ethics Board, conducted and interpreted the data analyses, and wrote the present thesis manuscript as well as both the individual study manuscripts. I performed the analyses for the systematic review of the

literature and I assisted with the statistical analyses for the cohort study manuscript, which were performed in SAS Analytics Software (version 9.4). For the systematic review of the literature, I extracted the relevant articles based on prespecified criteria and assessed the quality of the included studies. I have presented individual components of this work at the International Society on Thrombosis and Haemostasis (ISTH) 2021 meeting, the McGill University Clinician Investigator Program Research Day in 2021, the International Society of Obstetric Medicine (ISOM) 2022 meeting, the Groupe d'étude en médecine obstétricale du Québec (GEMOQ) 2022 meeting, the Canadian Venous Thromboembolism Research Network (CanVECTOR) 2022 meeting, the McGill University General Internal Medicine Symposium on the Management of Anticoagulants in 2022 and the American Society of Hematology (ASH) 2022 meeting. I am the recipient of the CanVECTOR studentship award (2020-2021) and the CanVECTOR fellowship award (2021-2022) for this work.

Drs. Vicky Tagalakis, MD, M.Sc. and Isabelle Malhamé MD, M.Sc.

My thesis supervisor, Dr. Vicky Tagalakis, and my thesis co-supervisor, Dr. Isabelle Malhamé provided content expertise and critical revisions of the entirety of the thesis work. They assisted with the conception of the research question, the protocol creation and study methodology. They both reviewed individual manuscripts as well as the entirety of this thesis manuscript. They provided content and methodological expertise.

Dr. Antonios Douros, MD, PhD

Dr. Antonios Douros provided guidance with regards to the methodology for both studies. He provided meaningful commentary with regards to bias assessment in the systematic

review, as well as guidance with the creation of the patient cohort for the second manuscript. Dr. Douros has reviewed individual manuscripts as well as the present thesis manuscript.

Dr. Kristian B. Filion, PhD

Dr. Kristian Filion provided critical revisions to both manuscripts and guidance with regards to the bias assessment of the systematic review. He has reviewed the present thesis manuscript and has provided meaningful commentary.

Dr. Hain Abenhaim, MD, M.Sc.

Dr. Haim Abenhaim provided critical revisions as a maternal-fetal-medicine content expert on the cohort study, as well as the present thesis manuscript.

Christopher Filliter, M.Sc.

Mr. Filliter created the study cohort for the cohort study manuscript following an established algorithm. He performed the statistical analyses for the cohort study using SAS Statistical Software (version 9.4). He provided meaningful comment on data interpretation for the entire thesis.

Dr. Lindsey Gerstein, MD

Dr. Gerstein was the second extractor for the systematic review of the literature. She performed this work independently of my primary data extraction. She also provided commentary on the systematic review manuscript.

Dr. Teresa Cafaro, MD

Dr. Cafaro performed the quality assessment of the included studies for the systematic review of the literature. She performed this independently of my primary assessment of the quality of the included studies using the ROBINS-I tool. She also provided meaningful commentary on the content of the systematic review manuscript.

Geneviève Gore

Ms. Gore is a librarian at the Schulich Library of Physical Sciences, Life Sciences, and Engineering at McGill University and she helped with the search strategy for the systematic review of the literature.

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LIST OF ABBREVIATIONS

American College of Obstetricians and Gynecologists	ACOG
Bis in die (latin) or twice daily	BID
Classification canadienne des actes diagnostiques, thérapeutiques et chirurgicaux	CCADTC
Classification canadienne des interventions en santé	CCI
Confidence internal	CI
Chronic kidney disease	CKD
Clinically relevant non-major bleeding	CRNMB
Cesarian section	CS
Quaque die (latin) or once daily	DIE
Direct oral anticoagulant	DOAC
Deep vein thrombus	DVT
Hazard ratio	HR
International Statistical Classification of Diseases and Related Health Problems	ICD
Intensive care unit	ICU
Institut de la statistique du Québec	ISQ
International Society on Thrombosis and Haemostasis	ISTH
Intention-to-treat	ITT
International unit	IU
Intravenous heparin	IVH
Kilograms	kg
Low-molecular-weight heparin	LMWH

Maintenance et exploitation des données pour l'étude de la clientèle hospitalière	MEDÉCHO
Milligrams	mg
Milliliters	mL
Non available	NA
Not included	NI
Odds ratio	OR
Pulmonary embolism	PE
Postpartum hemorrahge	PPH
Person-years	PY
Régie de l'assurance maladie du Québec	RAMQ
Reference	Ref
Relative risk	RR
Subcutaneous	SC
Standard deviation	SD
Total dispensed dose	TDD
Unfractionated heparin	UFH
Vaginal delivery	VD
Vitamin K antagonists	VKA
Venous thromboembolism	VTE
World Health Organization	WHO

INTRODUCTION

Venous thromboembolism (VTE), which comprises pulmonary embolism (PE) and deep vein thrombosis (DVT) is an important cause of maternal morbidity and mortality (1). Left untreated, VTE can be fatal (1). The treatment of VTE in pregnancy is therapeutic-dose anticoagulation with subcutaneous low-molecular-weight heparin (LMWH) for a minimum of three months, with treatment usually continued until six weeks postpartum (2). Variable estimates are reported in the literature pertaining to the risk of bleeding in pregnant patients treated with LMWH (3, 4). Studies evaluating bleeding in anticoagulated women during pregnancy have combined various doses and indications for anticoagulation, and bleeding definitions used are variable (5, 6). Moreover, the available studies are generally small, single centre retrospective cohort study with high risk of biases (4, 7). The first objective of my thesis was to summarize the literature with regards to the bleeding complications in patients treated with therapeutic-dose LMWH for the treatment of VTE during pregnancy by means of a systematic review of the literature and highlight the limitations of the existing literature. Given variable estimates of bleeding in the literature and variable clinical practice (8), the second objective of my thesis was to obtain population-derived estimates of bleeding complications in women treated for VTE during pregnancy using administrative healthcare databases.

Individual LMWHs, including dalteparin, enoxaparin and tinzaparin, are considered as having similar anticoagulant properties. They differ in their pharmacodynamic and pharmacokinetic properties, and this may impact anticoagulant-related bleeding risks (9). Canadian utilization for LMWHs in the general population has shown that over 50% of prescriptions dispensed are for dalteparin (10). Since dalteparin is the preferred LMWH, and

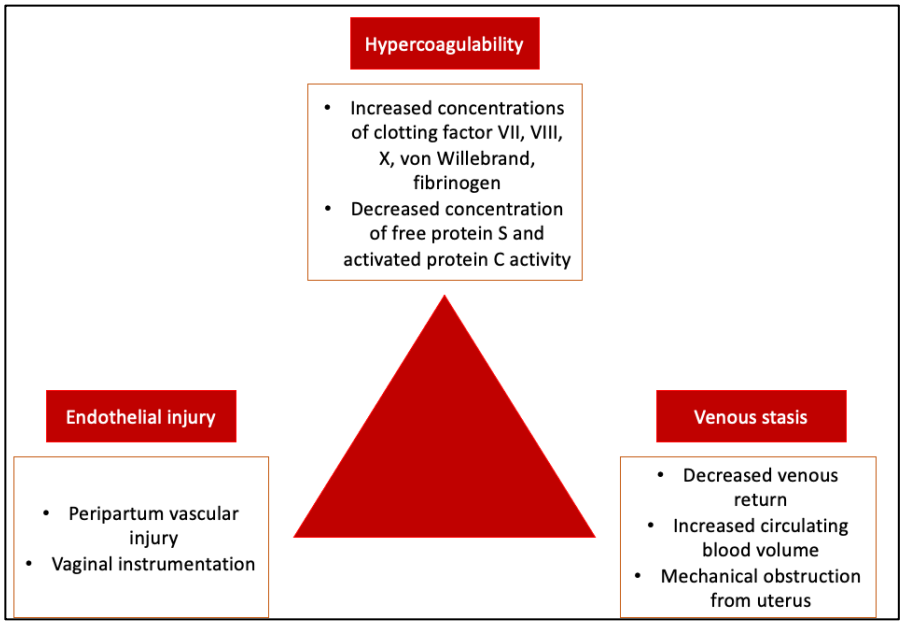
individual LMWHs may have different safety profiles, determining whether dalteparin confers a benefit regarding bleeding complications is important. To this end, the third objective of my thesis was to compare population-derived estimates of bleeding associated with the use of dalteparin vs. enoxaparin or tinzaparin in this population.

CHAPTER 1. BACKGROUND AND COMPREHENSIVE REVIEW OF THE LITERATURE

1.1 Epidemiology and pathophysiology of venous thromboembolism in pregnancy

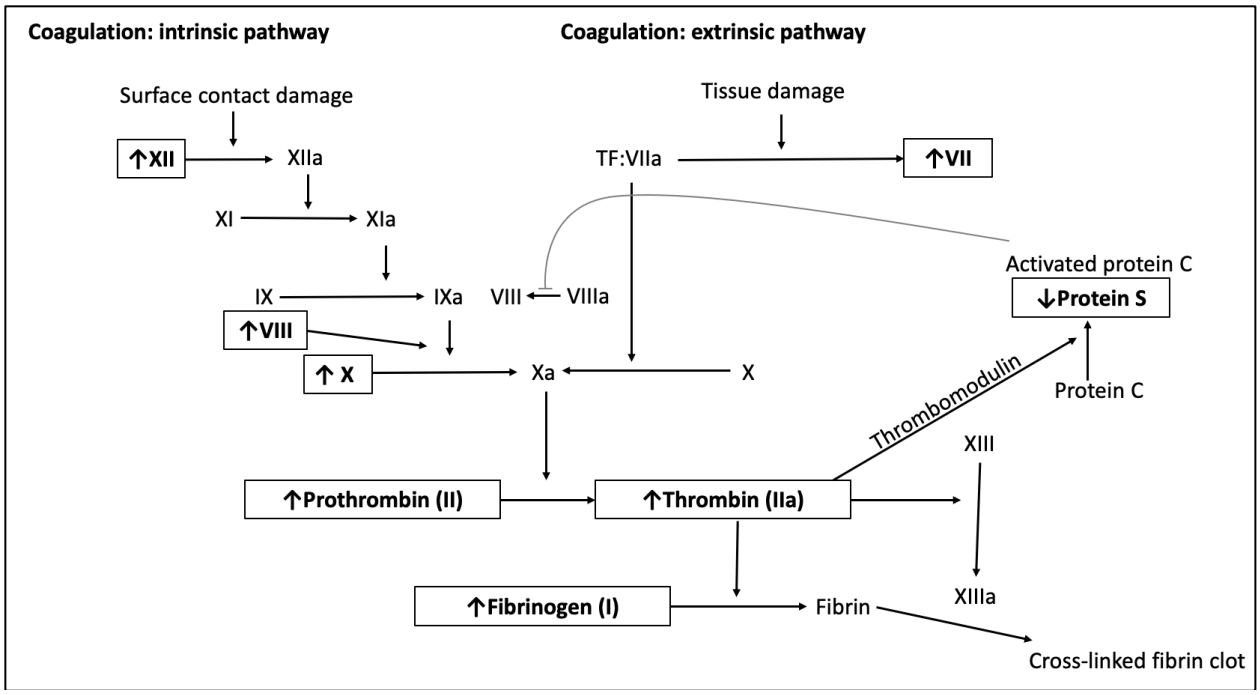
VTE describes the diagnoses of DVT and PE. DVT is the formation of thrombi in the deep venous system, commonly of the larger caliber veins in the lower extremities or the pelvis (11). Thrombus formation depends on the presence of abnormalities of blood flow, of the blood vessel wall and of blood clotting components (12). PE develops when a thrombus dislodges from clots in the vein wall and travel through the heart to the pulmonary arteries (11). Women are higher risk of VTE during pregnancy and the postpartum period (13). Pregnancy represents a hypercoagulable state resulting from hormonally induced decreased venous capacitance, decreased venous return, increased concentrations of coagulation factors and peripartum vascular injury (Figure 1) (14).

Figure 1. Physiologic changes in pregnancy that lead to an increased risk of venous thromboembolism (15)



Normal pregnancy leads to an increase in coagulation factors (factor VII, VIII, X and von Willebrand factor), as well as a significant increase in fibrinogen (1). The active, unbound form of protein S is decreased during pregnancy, and resistance to activated protein C is increased during the second and third trimesters, both of which contribute to a prothrombotic state (1) (Figure 2). The changes in coagulation factors in pregnancy are presented in Figure 2 (16). They begin at conception and return to normal in the 6 to 12 weeks following delivery (1).

Figure 2. Changes in coagulation pathway factors during pregnancy* (16)

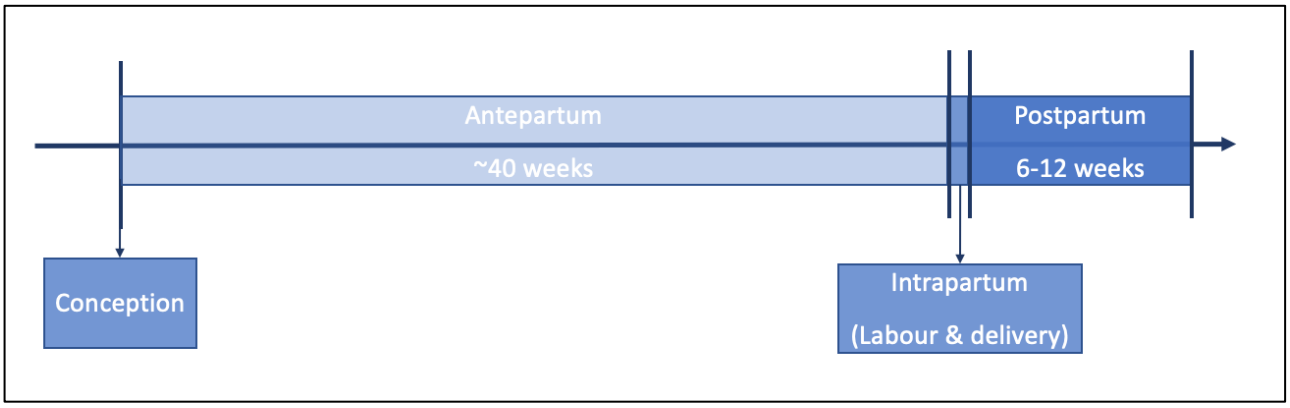


**Clotting factor that have significant changes are displayed with arrows. Abbreviations: TF=tissue factor.*

The antepartum period corresponds to the time between conception and delivery (17). The intrapartum period represents the time between the start of labour and the end of the delivery (17). While the postpartum period starts following delivery, its end is less well defined. It is often considered to be until six weeks following delivery. However, all organ systems do not

return to baseline within this period, and some consider the postpartum period to extend until 12 weeks after birth (Figure 3) (18).

Figure 3. Antepartum, intrapartum and postpartum periods (17)

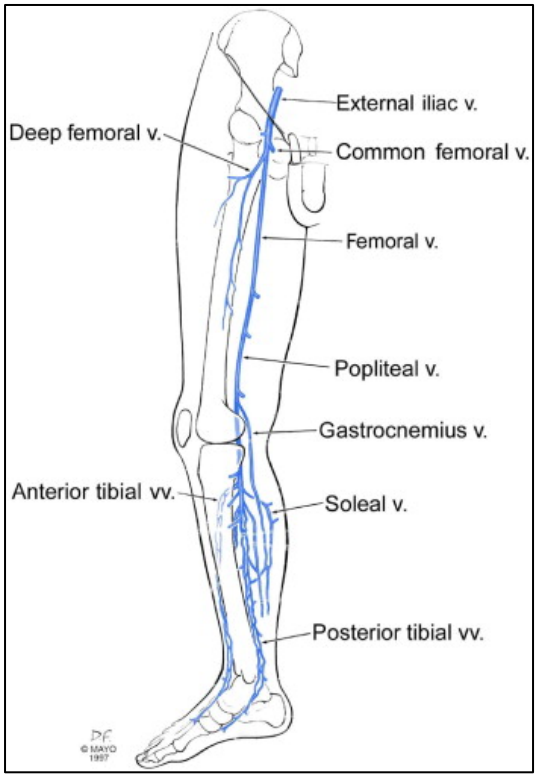


VTE is a leading cause of severe maternal mortality worldwide (19). It is estimated that VTE complicates 1 to 2 of 1000 pregnancies (20). The risk of VTE during pregnancy is increased five to ten-fold compared to non-pregnant women of comparable age (21). The risk is distributed across all three trimesters, although it appears to be highest in the third trimester (22). The absolute incidence of VTE is equal between the antepartum and postpartum periods, at 0.6 per 1000 women (22). However, because the postpartum period is shorter than the antepartum period, the daily risk of VTE during the first 6 weeks postpartum is higher in the postpartum than the antepartum period (23). The risk of VTE is increased until 12 weeks postpartum when compared to the general population, but women are at highest risk within the first 6 weeks postpartum (23).

1.2 Complications of venous thromboembolism during pregnancy

Numerous short and long-term complications are associated with VTE. Left untreated, VTE can be fatal. PE can lead to life threatening complications including chronic thromboembolic pulmonary hypertension, a cause of chronic pulmonary hypertension leading to right heart failure and death (24). In addition, VTE is also a cause of long-term morbidity in this population. Almost half of pregnant women with DVT will experience a reduced quality of life due to post-thrombotic syndrome (2). Post-thrombotic syndrome is a chronic complication that develops in 20 to 50% of patients after DVT and manifestations vary from mild to more severe symptoms and signs including chronic leg pain, intractable swelling or edema, and leg ulcers (25). Risk factors for post-thrombotic syndrome include older age, recurrent ipsilateral DVT, obesity and extensive DVT that affects large vessels (25). Pregnant women with DVT are at increased risk of post thrombotic syndrome because thrombosis in pregnancy predominantly affect larger caliber iliac or iliofemoral veins rather than the below knee smaller caliber vessels (Figure 4) (2). Moreover, women with VTE in pregnancy are at increased risk of recurrence in subsequent pregnancies, with recurrence rates ranging from 2.5% to 8% despite thromboprophylaxis (2). The risk of recurrence is decreased by prophylactic anticoagulation, with a reported rate of recurrent VTE between 0% and 2.4% with its use (1).

Figure 4. Deep venous system of the lower extremity (26)



Abbreviations: v=vein, vv=veins.

1.3 Treatment of venous thromboembolism during pregnancy

During pregnancy, subcutaneous weight-adjusted LMWH is the standard anticoagulation therapy for acute VTE (27, 28). Anticoagulant therapy markedly reduces mortality and the risk of VTE recurrence in the pregnant population (23). Women receive a minimum of three months of LMWH with treatment generally extended throughout pregnancy and for at least six weeks following delivery given the additional increased VTE risk during the postpartum period (27-30). In the non-pregnant population, other anticoagulants are used for the treatment of VTE, including vitamin K antagonists and direct oral anticoagulants. However, their use during pregnancy is constrained by the increased risk of teratogenicity associated with the use of

vitamin K antagonist and the limited data regarding the safety profile of direct oral anticoagulants (23). Unfractionated heparin (UFH) can be used as an intravenous infusion while patients are hospitalized.

LMWHs are a family of antithrombotic molecules derived from UFH by chemical or enzymatic depolymerization (31). The smaller molecular size of LMWHs results in increased bioavailability and a longer half-life compared to UFH (32). Subcutaneous UFH has a similar safety profile with regards to fetal safety, but it is associated with a higher risk of heparin-induced thrombocytopenia (HIT), a prothrombotic disorder associated with the use of heparins characterized by thrombocytopenia and a high risk of venous or arterial thrombosis (2, 33). Fondaparinux, a synthetic anticoagulant that indirectly inhibits factor Xa (Figure 6), crosses the placenta and experience in human pregnancies is limited. It is occasionally used in pregnancy when a type I allergy to LMWH is suspected or in the context of HIT (2). LMWHs used during pregnancy include enoxaparin, dalteparin and tinzaparin. Different LMWH agents have similar antithrombotic effects. However, different they have distinct biochemical and pharmacological profiles (Table 4) (34). Four LMWH agents are approved by Health Canada for the treatment of VTE, but only three are marketed for use. These are dalteparin, enoxaparin and tinzaparin (10). These tend to be used interchangeably, depending on availability in each centre.

1.4 Bleeding associated with therapeutic anticoagulation for venous thromboembolism during pregnancy

Variable estimates are reported in the literature pertaining to the risk of bleeding in pregnant patients treated with therapeutic anticoagulation for VTE (Table 1). Most studies report

on bleeding during the immediate postpartum period of the pregnancy which is defined as within 24 hours of delivery (4). While some studies use postpartum hemorrhage (PPH), defined as bleeding greater than a specific cut-off (500 or 1000 mL) within 24 hours of delivery, as a main bleeding outcome (3, 4), other studies (6, 7) use a composite outcome of major bleeding from the International Society on Thrombosis and Haemostasis (ISTH) which comprises fatal bleeding and/or bleeding in a critical area or organ, and/or bleeding causing a fall in hemoglobin level of 20 g/L or leading to a transfusion of two or more units of whole blood or red cells (35). This definition was established in an attempt to standardize bleeding definitions and has been extensively used in research (35), but it is not well suited for pregnancy-related bleeding events such as antepartum and postpartum bleeding, including PPH (36). There is also variation in the definition of PPH, with some studies using different blood loss thresholds within the first 24 hours postpartum according to the mode of delivery (3), while other studies do not make that distinction (4). Reported major bleeding events according to the ISTH definition of major bleeding range between 2.9 and 5.0% in women receiving therapeutic anticoagulation during pregnancy (6, 7). Reported estimates of PPH in the literature vary. While some studies showing an increased risk of PPH in patients receiving therapeutic anticoagulation, others do not (3, 4). Moreover, while some studies report both antepartum and postpartum bleeding events (6, 7), others report only on the risk of PPH (3, 4). As such, the available literature does not provide reliable bleeding estimates and fails to accurately inform clinicians as to whether the risk of clinically significant blood loss is increased with the use of anticoagulation during pregnancy.

Table 1. Studies evaluating bleeding outcomes for pregnant women on therapeutic dose low-molecular-weight heparin for venous thromboembolism

Study	Year of publication	Study design	Population size (n)	Control group size (n)	Intervention	Bleeding definition	Bleeding estimate
Blanco-Molina et al. (6)	2007	Prospective cohort study	136	NA	LMWH (type not specified)	ISTH definition of major bleeding (35)	**Major bleeding**: 4/136 (2.9%).
Chan et al. (7)	2012	Retrospective cohort study	60	NA	Once or twice daily LMWH (dalteparin or enoxaparin)	ISTH definition of major bleeding (35)	**Major bleeding**: 3/60 (5.0%, 95% CI 1.0-14.0%). 6 total bleeding events (6/60, 10.0%).
Côté-Poirier et al. (37)	2020	Retrospective cohort study	232	NA	Therapeutic dose LWMH (dalteparin, enoxaparin or tinzaparin) or IVH	Major hemorrhagic complication*	**Major hemorrhagic complication**: 9/149 (6.0%, 95% CI 2.8-11.1) for VD and 7/83 (8.4%, 95% CI 3.5-16.6) for CS.
Knol et al. (38)	2012	Retrospective cohort study	88	352	Therapeutic dose LMWH (nadroparin)	VD: PPH ≥ 500 mL, severe PPH ≥ 1000 mL CS: PPH ≥ 1000 mL	**PPH**: 30.0% vs. 18.0% in treatment vs. control group (OR 1.9, 95% CI 1.1-3.5) for VD and 12.0% vs. 4.0% in treatment vs. control group (OR 2.9, 95% CI 0.5-19.4) for CS. **Severe PPH**:5.6% vs. 5.0% (OR 1.1, 95% CI 0.4-3.6) for VD.

Roshani et al. (39)	2011	Retrospective cohort study	95	524	Therapeutic dose LMWH (enoxaparin, dalteparin, nadroparin, tinzaparin, danaparoid)	PPH > 500 mL, severe PPH > 1000 mL	**PPH**: 18.0% in treatment group vs. 22.0% in control group (RR 0.8, 95% CI 0.5-1.4). **Severe PPH**: 6.0% in both groups (RR 1.2 95% CI 0.5-2.9)

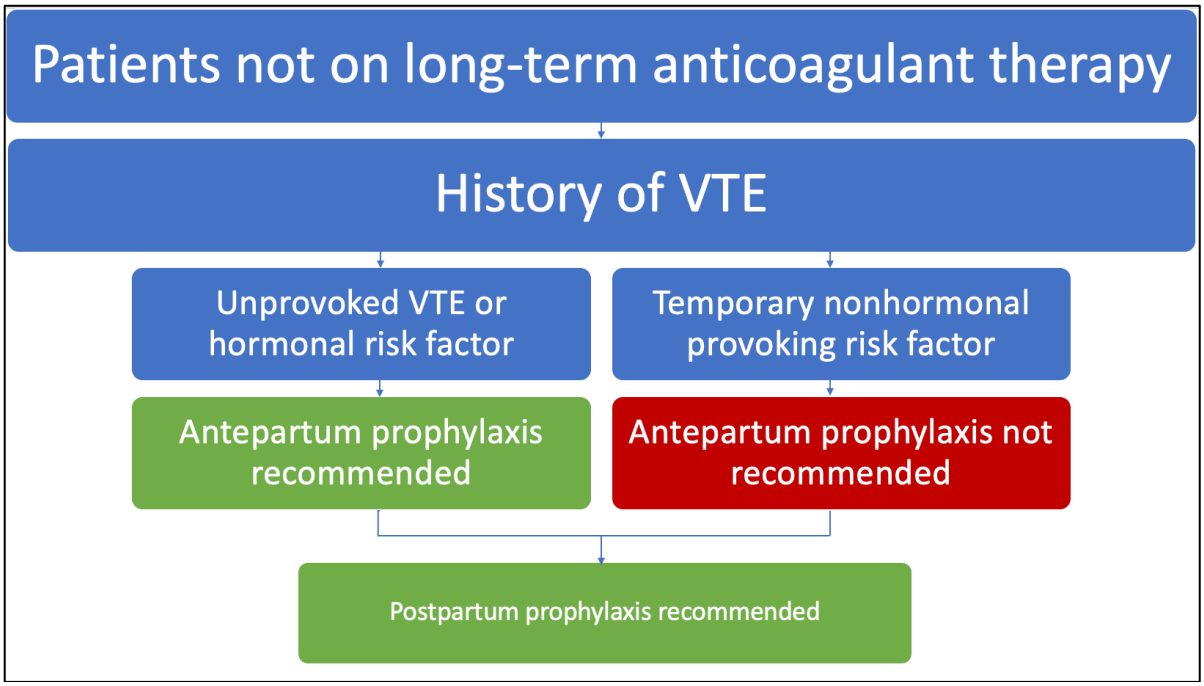
Abbreviation: CI = confidence interval, CS = cesarian delivery, ICU = intensive care unit, ISTH = International Society on Thrombosis and Haemostasis, IVH = intravenous heparin, LMWH =low-molecular-weight heparin, NA= non-available, OR = odds ratio, PPH = postpartum hemorrhage, VD = vaginal delivery.

**Major hemorrhagic complication defined as significant bleeding that occurred after the resumption of therapeutic anticoagulation requiring surgery, hospital readmission, admission to the intensive care unit, red blood cells transfusion, or fluid resuscitation of 1L or more of crystalloid (prescribed specifically for a bleeding concern after therapeutic anticoagulation resumption, so not related to the immediate intrapartum and postpartum period).*

1.5 Bleeding associated with different doses of low-molecular-weight heparin for venous thromboembolism during pregnancy

Previous studies have evaluated the risk of bleeding in women receiving LMWH during pregnancy, whereby authors commonly group pregnant patients receiving different doses of anticoagulation, either for the treatment or the prevention of VTE during pregnancy (40-42). Women who have a history of a VTE and who are not on long-term anticoagulant therapy require LMWH during pregnancy, usually at a prophylactic dose, to prevent a recurrence given the associated prothrombotic state (23, 28). If the previous event was due to a temporary provoking factor that is not related to a hormonal risk factor (e.g., pregnancy, postpartum state, hormonal contraception, or hormonal replacement therapy), then thromboprophylaxis is advised only during the postpartum period, usually until six weeks after delivery. If the previous event was either unprovoked or due to a hormonal risk factor, then both antepartum and postpartum thromboprophylaxis are recommended (23, 28). The recommendations are summarized in Figure 5.

Figure 5. Prophylaxis for pregnant women not receiving long-term anticoagulant therapy (23)



Abbreviation: VTE=venous thromboembolism.
Figure adapted from Bates et al, Journal of Thrombosis and Haemostasis, 2018.

Prophylactic dose LMWH usually is given at a standard fixed dose (e.g., dalteparin 5000 units subcutaneously every 24 hours) with adjustments for extremes of body weight (43). Previous studies have suggested that standard prophylactic dose LMWH commonly given in surgical patients and hospitalized patients may not adequately prevent VTE during pregnancy given the increased thrombotic risk of pregnancy (44). For this reason, some clinicians opt to administer intermediate dose thromboprophylaxis in high-risk pregnant patients (44). Examples of populations judged to be at higher risk of VTE include women with high-risk inherited thrombophilia (e.g., antithrombin deficiency or homozygote factor V Leiden) or women with two or more episodes of previous VTE who are not on long-term anticoagulation (44). Intermediate dose anticoagulation usually corresponds to half of the therapeutic dose (e.g.,

dalteparin 100 units/kg or enoxaparin 1 mg/kg once daily). The optimal dose of LMWH in this patient population remains unknown, and this has led to a randomized controlled trial which compared standard prophylactic and intermediate dose LMWH anticoagulation in specific high-risk pregnant populations (45). While there was no difference in the incidence of VTE between both dosing regimens, a post-hoc analysis showed a decrease in the numerical number of PE and superficial thrombophlebitis events with intermediate-dose LMWH in the postpartum period (45). Suggested thromboprophylactic doses for antepartum and postpartum LMWH according to body weight from the Royal College of Obstetricians and Gynecologists are presented in Table 2 (46). Intermediate and therapeutic doses for dalteparin, enoxaparin and tinzaparin are presented in Table 3.

Table 2. Prophylactic doses of LMWH according to body weight according to the Royal College of Obstetricians and Gynecologists (46)

Weight	Dalteparin	Enoxaparin	Tinzaparin
< 50 kg	2500 units daily	20 mg daily	3500 units daily
50-90 kg	5000 units daily	40 mg daily	4500 units daily
91-130 kg	7500 units daily	60 mg daily	7000 units daily
131-170 kg	10 000 units daily	80 mg daily	9000 units daily
> 170 kg	75 units/kg/day	0.6 mg/kg/day	4500 units every 12 hours

Abbreviations: kg=kilograms, mg=milligrams.

Table 3. Intermediate and therapeutic doses of low-molecular-weight heparin doses used in pregnancy (43)

Heparin	Dose Level	Dose
Dalteparin	Intermediate	Dalteparin 100 units/kg SC DIE
	Therapeutic	Dalteparin 200 units/kg SC DIE or 100 units/kg SC BID
Enoxaparin	Intermediate	Enoxaparin 1 mg/kg SC DIE
	Therapeutic	Enoxaparin 1 mg/kg SC every 12 hours or 1.5 mg/kg SC DIE
Tinzaparin	Intermediate	Variable
	Therapeutic	Tinzaparin 175 units/kg SC DIE

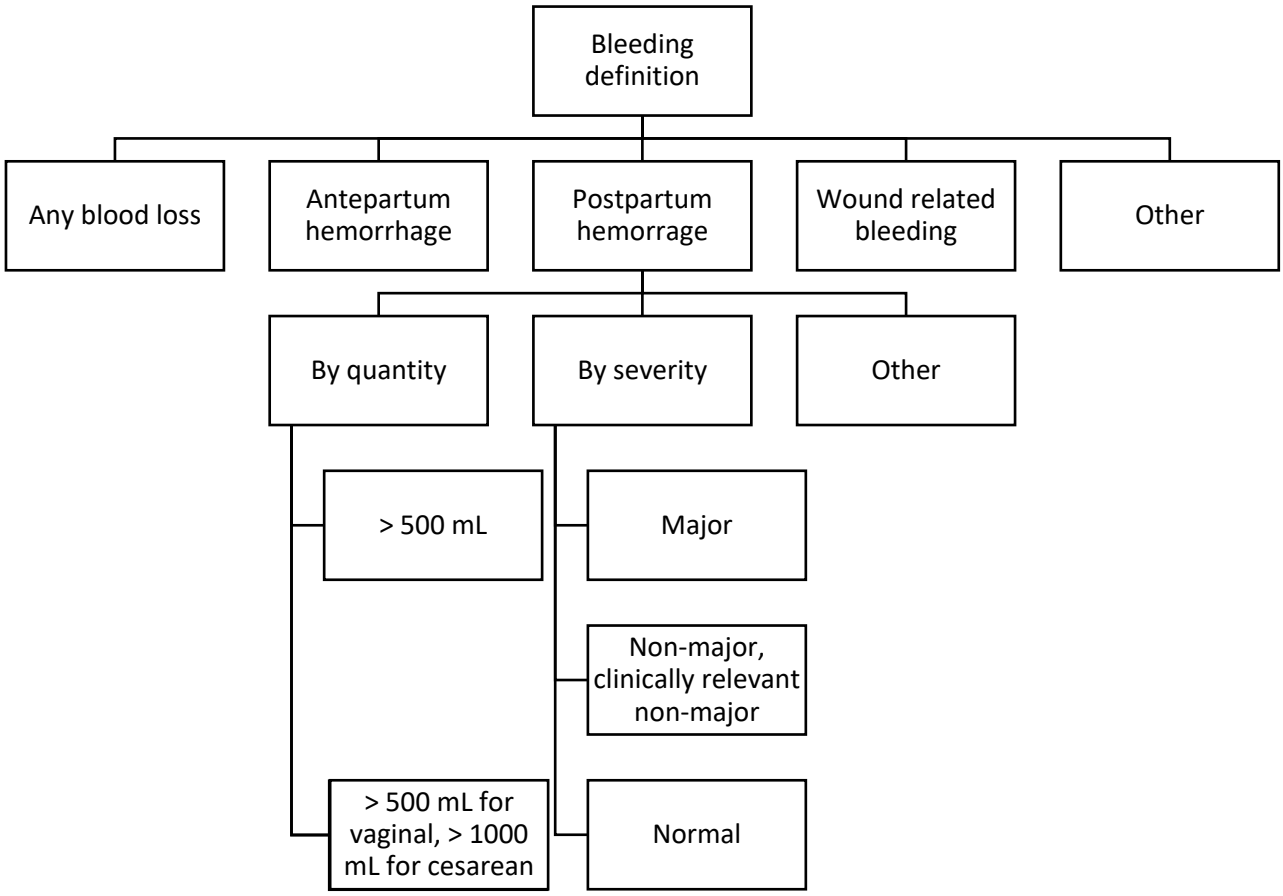
Abbreviations: BID= twice daily, DIE = once daily, kg=kilograms, SC= subcutaneous.

When assessing the safety of LMWHs and the risk of bleeding associated with their use during pregnancy, reported estimates of bleeding are also variable, regardless of the dose used. Selected studies presenting bleeding estimates of patients treated with variable doses of LMWH during pregnancy are presented in Table 4.

Moreover, there is a wide variation in the bleeding definitions used in the literature (Figure 6). Studies have reported bleeding events as PPH by estimated blood loss within 24 hours of delivery with variable cut-offs (3, 4). Others use the major bleeding and clinically relevant non-major bleeding according to the ISTH with different definitions for surficial and non-surgical major bleeding (35, 47) or various combinations of drop in hemoglobin level, need

for blood product transfusion, surgical intervention to control bleeding, need for intensive care unit admission, or wound complications (Figure 6) (37).

Figure 6. Definitions of bleeding in pregnancy reported in the literature (3, 4, 6, 7, 37, 48)



Abbreviation: mL=milliliters.

Table 4. Selected studies evaluating bleeding outcomes for pregnant women on variable doses low-molecular-weight heparin for venous thromboembolism

Study	Year of publication	Study design	Population size (n)	Control group size (n)	Intervention	Bleeding definition	Bleeding estimate in intervention vs. control group
Arbuthnot et al. (42)	2017	Retrospective cohort study	127	16,469	LMWH *Prophylaxis: 57.0% Therapeutic: 37.0%*	**PPH** ≥500 mL, **Severe PPH** ≥1000 mL	**PPH:** 22.6% vs. 21.6% **Severe PPH:** 3.4% vs. 4.8%
Galambosi et al. (49)	2011	Retrospective cohort study	475	648	LMWH at variable doses, proportion NR	**Major blood loss** > 1000 mL	**Major blood loss:** 6.8% vs. 4.5% (p=0.098)
Kominiarek et al. (48)	2007	Case control study	49	110	LMWH *Prophylaxis: 32.7% Therapeutic: 67.3%*	**PPH** > 500 mL for VD, > 1000 mL for CS or return to or for bleeding within 14 days of delivery	**PPH:** 11.0% vs. 8.2% (OR 1.37, 95% CI 0.15-11.5)
Santoro et al. (50)	2009	Prospective cohort study	114	NR	LMWH at variable doses, proportion NR	**Major bleeding:** decrease in hemoglobin of 2 g/dL or blood transfusion	**Major bleeding:** 1.53% (no control group)

Abbreviations: CI = confidence interval, CS = cesarian delivery, LMWH = low-molecular-weight heparin, NR = not reported, OR = odds ratio, PPH = postpartum hemorrhage, VD = vaginal delivery.

1.6 Need for population-based estimates of bleeding in women treated for venous thromboembolism during pregnancy

Five previously published systematic reviews have highlighted the variable and low-quality retrospective data evaluating bleeding in patients anticoagulated for various indications during pregnancy and the need for standardized bleeding definitions (36, 40, 41, 51, 52). The main findings of these systematic reviews are presented in Table 5. The five systematic reviews include women on variable doses of anticoagulation (prophylactic, intermediate, and therapeutic) for various indications (Table 5). These pooled bleeding estimates may be difficult for healthcare providers to interpret. For example, bleeding associated with the use of prophylactic-dose LMWH for a history of pregnancy losses that is stopped at 38 weeks' gestation is unlikely to be comparable to bleeding associated with the use of therapeutic-dose anticoagulation that is restarted early in the postpartum period in a patient with a mechanical heart valve given the risk of valve thrombosis with interruption of anticoagulation (52, 53). As such, population-based estimates of bleeding in pregnant women receiving therapeutic-dose anticoagulation for VTE are required to better guide clinician decisions and facilitate patient counselling.

Table 5. Previous systematic reviews evaluating bleeding complications in women treated with various doses of low-molecular-weight heparin for various indications

Study	Year of publication	Population size (n)	Comparator group size (n)	Indication for anticoagulation	Anticoagulant	Dose of anticoagulation	Bleeding estimate
Greer et al. (40)	2005	2777	NA	Treatment of VTE, thromboprophylaxis, prevention of recurrent pregnancy loss, prevention of preeclampsia/IUGR, unspecified	LMWH (enoxaparin, dalteparin, nadroparin, tinzaparin, certoparin, reviparin)	Therapeutic and prophylactic	**Significant bleeding**: 2.0% (95% CI 1.5-2.6%)
Romualdi et al. (51)	2012	981	NA	Treatment of VTE	LMWH (enoxaparin, dalteparin, nadroparin, tinzaparin) and UFH	Therapeutic	**Weight mean incidence of major bleeding**: 1.4% (95% CI 0.6-2.4%)
Sanson et al. (52)	1999	486	NA	Treatment of VTE, thromboprophylaxis, prevention of recurrent pregnancy loss, prevention of preeclampsia, thrombophilia, mechanical heart	LMWH (enoxaparin, dalteparin, nadroparin, tinzaparin, reviparin)	Prophylactic, intermediate, therapeutic	**Clinically important hemorrhagic complication**: none **Minor bleeding**: 2.7% (95% CI 1.4-4.5%)

				valves, miscellaneous			
Sirico et al. (41)	2019	1320	20842	Treatment of VTE, thromboprophylaxis, prevention of recurrent pregnancy loss, prevention of preeclampsia, thrombophilia, mechanical heart valves, miscellaneous	LMWH (enoxaparin, dalteparin, nadroparin, tinzaparin)	Prophylactic, therapeutic, not reported	**PPH***: increased in women treated with LMWH, RR 1.45 (95% CI 1.0-2.1%) No difference in mean blood loss or risk of transfusion at delivery between groups.
Tardy et al. (36)	2019	2690	NA	Recurrent pregnancy loss, obstetrical antiphospholipid syndrome, placental vascular complications, preeclampsia/IUGR, thrombophilia	LMWH (enoxaparin, dalteparin, nadroparin), UFH	Prophylactic	**Major antepartum bleeding**: 0.0-9.7% **Major or severe PPH**: 1.0-5.6%

*PPH is defined differently in various studies. *Abbreviations: CI= confidence interval, IUGR= intrauterine growth restriction, LMWH = low-molecular-weight-heparin, n= number of patients, NA = not available, PPH = postpartum hemorrhage, RR = relative risk, VTE= venous thromboembolism, UFH = unfractionated heparin.*

1.7 Need for population-based estimates of bleeding in women treated with different types of LMWH during pregnancy

LMWHs are considered members of a class of drugs with similar anticoagulant properties (54). They act by inhibiting the final common pathway of the coagulation cascade (Figure 7). Specifically, they activate antithrombin III, which binds and inhibits factor Xa preventing clot formation (Figure 7) (55). However, LMWHs differ in their pharmacodynamic and pharmacokinetic properties, and this may impact the rates of anticoagulant-related bleeding (9). For example, the half-life of the anti-Xa activity varies between different LMWHs (Table 6) (54). Moreover, pregnancy can affect the pharmacologic characteristics of individual LMWHs. Among non-pregnant people, LMWHs have low volumes of distribution, which means that they are essentially confined to the bloodstream. However, pharmacokinetic studies conducted among pregnant people have shown an increase in the volumes of distribution of LMWHs. Combined with the increase in body weight during pregnancy, the change in the volume of distribution could theoretically lead to lower drug plasma levels. This phenomenon could be further augmented by the increased renal elimination of LMWHs during pregnancy due to an elevated glomerular filtration rate (21).

In the non-pregnant population, evidence with regards to bleeding risks using different LMWHs has been contradictory (56-59). In a retrospective cohort study of patients admitted to the intensive care unit receiving enoxaparin or dalteparin for VTE prophylaxis, there was no difference in the percentage of patients diagnosed with major bleeding between the two groups (56). A prospective, randomized, open-labeled, single-center study of patients with non-ST-

segment elevation myocardial infarction (NSTEMI) receiving either therapeutic enoxaparin or tinzaparin showed no difference in the percentage of serious hemorrhagic complications between groups (3.6% in the enoxaparin group vs. 3.2% in the tinzaparin group, p-value not reported) (60). Finally, a large randomized controlled trial of over 20 000 patients with NSTEMI found that the use of fondaparinux was associated with lower rate of major bleeding compared to enoxaparin (2.2% vs. 4.1%, p<0.001) (58). No studies have compared the frequency of bleeding complications during pregnancy across different LMWH groups. While dalteparin is the most commonly used LMWH in Canada, it has not been shown to confer a favourable safety profile compared to other LMWHs (10). For this reason, population-derived bleeding estimates addressing the risk of bleeding according to LMWH type are warranted given the variable pharmacokinetic and pharmacodynamic properties which may have differential effects on the risk of bleeding.

Figure 7. Coagulation cascade and effect of anticoagulant medications (61)

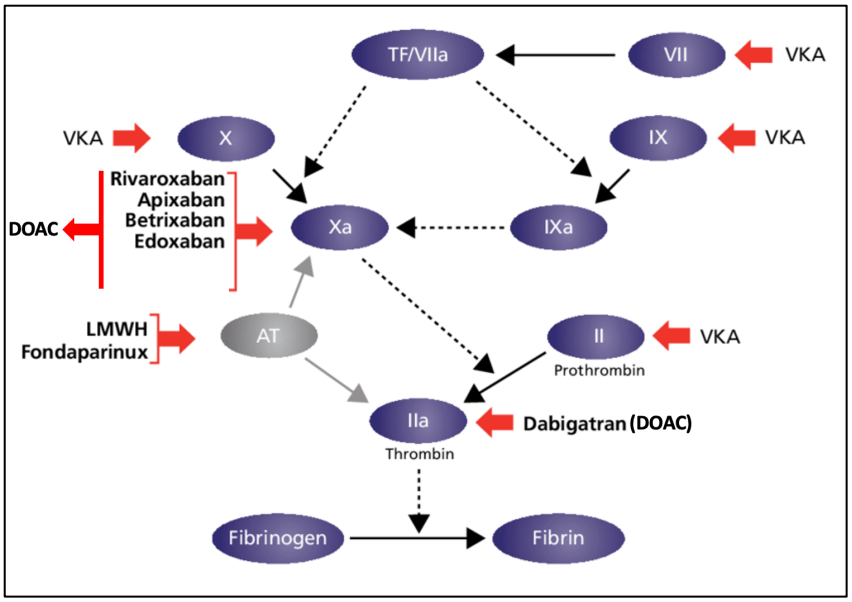


Figure adapted from Hoppe-Tichy et al. EJHP Practice, 2010. (61)

Solid black arrows represent transformations; dashed black lines represent catalysis
Abbreviations: AT= antithrombin, DOAC= direct oral anticoagulant, LMWH= low-molecular-weight heparin, TF= tissue factor, VKA= vitamin K antagonist.

Table 6. Pharmacological properties of low molecular weight heparins (34, 62, 63)

	Enoxaparin	**Dalteparin**	**Tinzaparin**
Dosage for therapeutic anticoagulation	1.5 mg/kg subcutaneous (SC) once daily (DIE) or 1 mg/kg SC twice daily (BID)	200 U/kg SC DIE	175 U/kg SC DIE
Mean molecular weight (daltons)	4500	5800	6500
Elimination half-life (hours)	4.3	2.4	3.0
Bioavailability (%)	90-92	87	87
Anti-Xa activity (IU/mg)	100	156	100

Abbreviations: IU= international units, kg=kilograms, mg=milligrams.

1.8 Original thesis work

Thesis objectives

The present thesis has three primary objectives:

1. To summarize the literature with regards to the bleeding complications in patients treated with therapeutic-dose LMWH for the treatment of VTE during pregnancy, and highlight the limitations of this literature
2. To obtain population-derived estimates of bleeding complications in women treated for venous thromboembolism during pregnancy

3. To compare population-derived estimates of bleeding associated with the use of dalteparin vs. enoxaparin or tinzaparin in women treated for VTE during pregnancy

Thesis overview

Chapter 2 will include the first manuscript of my thesis. It will consist of a systematic review of the literature with a focus on patients treated with therapeutic-dose anticoagulation for a VTE during pregnancy, with a defined bleeding outcome. Chapter 3 will include a transition between the findings of the systematic review and explain the rationale for the second manuscript. Chapter 4 will include the cohort study manuscript. This will provide population-derived estimates of bleeding in this patient population, as well as a comparison of bleeding estimates between the most used LMWH, dalteparin, vs. enoxaparin or tinzaparin. Chapter 5 will discuss the main findings of this thesis, its limitations, and promising tools for future research. Chapter 6 will include conclusions for the study of bleeding complications in this patient population.

CHAPTER 2. LITERATURE REVIEW

2.1 Preface to first manuscript

The risk of bleeding associated with the use of therapeutic anticoagulation for VTE during pregnancy, including during the antepartum and postpartum periods, is not well described. Systematic reviews evaluating bleeding in patients treated for VTE during pregnancy have combined different doses (prophylactic, intermediate and therapeutic-dose anticoagulation) of LMWH anticoagulation (40, 41). Other review articles have combined multiple indications for anticoagulation during pregnancy, including mechanical heart valves and thrombophilia without VTE (41, 64). The risk of bleeding in these different populations is not considered to be the same, given different comorbidities and comedications. For these reasons, we decided to conduct a systematic review of the literature evaluating bleeding complications in pregnant women treated for VTE with therapeutic-dose anticoagulation during pregnancy. The limitations and the high risk of bias in the available literature are highlighted in the discussion section of the manuscript.

2.2 Systematic review manuscript

Bleeding Complications in Women with Venous Thromboembolism during Pregnancy: A Systematic Review of the Literature

Simard C[1], Gerstein L[2], Cafaro T[1], Filion KB[3], Douros A[3], Malhamé I[4,5], Tagalakis V[1,3], for the Canadian Venous Thromboembolism Clinical Trials and Outcomes Research (CanVECTOR) Network

[1]Division of General Internal Medicine, Department of Medicine, Jewish General Hospital, McGill University, Montreal, Canada, [2]Department of Medicine, McGill University, Montreal, Canada, [3]Centre for Clinical Epidemiology of the Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, Canada, [4]Division of General Internal Medicine, Department of Medicine, McGill University Health Centre, McGill University, Montreal, Canada, [5]Research Institute of the McGill University Health Centre, Montreal, Canada.

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Corresponding author:
Dr. Camille Simard
Division of General Internal Medicine, Jewish General Hospital
3755 Côte-Sainte-Catherine, Rm G-050
Montreal, Québec, Canada
H3T 1E2
Tel: 1-514-340-8222
Email: camille.simard@mail.mcgill.ca

CONFLICT OF INTEREST DISCLOSURE

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Dr. Antonios Douros: no conflict of interest to declare.

Dr. Isabelle Malhamé: no conflict of interest to declare.

Dr. Vicky Tagalakis: no conflict of interest to declare.

AUTHOR CONTRIBUTION

Conceptualization: Camille Simard, Isabelle Malhamé, Vicky Tagalakis.

Methodology: Camille Simard, Isabelle Malhamé, Antonios Douros, Kristian Filion, Vicky Tagalakis.

Formal analysis and investigation: Camille Simard, Lindsey Gerstein, Teresa Cafaro, Isabelle Malhamé

Original draft preparation: Camille Simard, Isabelle Malhamé, Vicky Tagalakis

Review and editing: Camille Simard, Lindsey Gerstein, Teresa Cafaro, Kristian Filion, Antonios Douros, Isabelle Malhamé, Vicky Tagalakis

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ESSENTIALS

- In pregnancy, blood clots, or venous thromboembolism (VTE), are treated with blood thinners.
- The risk of bleeding with the use of blood thinner in pregnancy is not well described.
- There was a wide range of bleeding complications in this review, between 2.9% and 30.0%.
- Larger studies looking at this question are needed to better inform patients and doctors.

ABSTRACT

OBJECTIVES

Venous thromboembolism (VTE) represents an important cause of maternal morbidity and mortality. Estimates of bleeding associated with therapeutic-dose anticoagulation are variable. We describe the frequency of bleeding in pregnant women receiving therapeutic anticoagulation for VTE by means of a systematic review of the literature.

DATA SOURCES

MEDLINE, Embase, Scopus, Web of Science and ClinicalTrials.gov were searched. Databases were searched from inception to February 27, 2022. There was no language or geographic location restriction.

METHODS OF STUDY SELECTION

The search yielded 2773 articles with 2212 unique citations. Studies were included if they described pregnant women treated for an acute VTE with therapeutic-dose anticoagulation and a defined bleeding outcome was reported.

TABULATION, INTEGRATION, AND RESULTS

Five studies met inclusion criteria. Included studies were judged to have a serious to critical risk of bias using the ROBINS-I tool. The rate of bleeding, as defined by respective studies, ranged between 2.9% and 30.0%. Two studies included control groups, one of which found no significant difference in the risk of bleeding between groups, while the other found a significantly increased bleeding risk associated with therapeutic anticoagulation.

CONCLUSION

Among pregnant women anticoagulated for VTE, the reported bleeding risk is variable. The ability to draw definite conclusions is limited by the scarcity and low quality of the studies, the small number of included patients, and the heterogeneity of bleeding definitions used. Large scale studies with standardized bleeding definitions are required to provide acute bleeding estimates and optimize the care of these patients.

SYSTEMATIC REVIEW REGISTRATION:

PROSPERO, CRD42021276771

KEYWORDS

Venous thromboembolism; Pregnancy; Hemorrhage; Anticoagulation.

INTRODUCTION

Women are at an increased risk of venous thromboembolism (VTE) during pregnancy and the postpartum period. VTE, which includes pulmonary embolism (PE) and deep vein thrombosis (DVT), complicates 1 to 2 of 1000 pregnancies and is an important cause of maternal morbidity and mortality (1). The risk of VTE is 10- to 20-fold higher in pregnancy than in matched non-pregnant women (2). The increased risk of thrombosis reflects physiological changes during pregnancy resulting in hormonally induced decreased venous capacitance, decreased venous outflow, increased concentrations of coagulation factors and peripartum vascular injury (3).

Weight-adjusted subcutaneous low-molecular-weight heparin (LMWH) is the standard anticoagulant therapy both for the prevention and the treatment of VTE during pregnancy (4, 5). Therapeutic dose anticoagulant therapy reduces mortality and the risk of VTE recurrence in the pregnant population (6, 7). While LMWH is considered safe in pregnancy, variable estimates are reported in the literature pertaining to the risk of bleeding with the use of therapeutic anticoagulation for VTE in pregnancy (8-10). Postpartum hemorrhage (PPH) is the leading direct cause of maternal death worldwide (11). As such, understanding the risk of bleeding for women on therapeutic anticoagulation is paramount to inform clinical care and anticipate the healthcare needs of this complex population.

Previous studies have evaluated the risk of bleeding associated with the use of LMWH in pregnancy. Reviews in the area either combined data from patients receiving different doses and indications for LMWH (12, 13) or focused on the therapeutic efficacy rather than the bleeding complications associated with the use of LMWH for VTE (14). The aim of the current systematic

review was to evaluate the risk of antepartum and postpartum bleeding in women receiving therapeutic anticoagulation for VTE during pregnancy.

MATERIAL AND METHODS

This systematic review was conducted according to a prespecified protocol following the reporting guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (15). The protocol was registered on PROSPERO (CRD42021276771) (16). Review objectives, criteria for study selection and bias assessment method were defined *a priori*.

Sources

A search strategy was developed in conjunction with a medical librarian. An electronic search was conducted from database inception to February 27, 2022, using the following databases: Medical Literature Analysis and Retrieval System (MEDLINE), Excerpta Medical Database (Embase), Scopus, Web of Science and ClinicalTrials.gov. The search strategy was based on two key concepts: (1) anticoagulation using key words including "heparin", "low molecular weight heparin" and (2) bleeding using key words such as "antepartum" or "postpartum hemorrhage" (Appendix A). The search strategy was adapted for each database based on its specific nomenclature. There was no language or geographic location restriction applied. A manual search of the reference lists of all included studies and relevant review articles was additionally performed. All results were imported into an EndNote X9 library to remove duplicates and then transferred into Distiller SR (*DistillerSR*. Version 2.35. Evidence Partners; 2021) to ensure rigorous methodology and reporting.

Study selection

Included studies (1) described women treated for an acute VTE during pregnancy (2) receiving weight-adjusted therapeutic-dose anticoagulation with LMWH, and (3) reported a defined bleeding outcome. Bleeding events during the antepartum and postpartum periods, as defined by the study, were evaluated. Studies where the main indication for therapeutic anticoagulation was not VTE (e.g., anticoagulation for mechanical heart valve) or the dose of anticoagulation used was not therapeutic (i.e., prophylactic or intermediate dose) were excluded. Studies including populations with mixed indications for therapeutic anticoagulation (e.g., VTE and antiphospholipid syndrome) were included so long as the majority of included patients (i.e., > 50.0%) were treated for VTE. Case reports, editorials, commentaries, conference abstracts and review articles were excluded. The articles identified in the literature search were screened by title and abstract by two independent reviewers (CS, LG). Articles deemed potentially relevant were retrieved for full-text review. Discrepancies during full-text review were resolved through discussion and by the opinion of a third reviewer (IM) when necessary.

Data extraction and quality assessment

An electronic data extraction form was developed and used by two independent reviewers (CS, LG). Disagreements were resolved by consensus or by a third reviewer (IM). Study and patient characteristics, intervention and outcome definitions were collected. Clinical bleeding outcomes, as defined by investigators in each study, were extracted.

The Risk of Bias in Non-randomized Studies of Intervention (ROBINS-I) tool was used for quality assessment by two independent reviewers (CS, TC) (17). Disagreements were resolved by consensus. The ROBINS-I tool was selected as it provides a comprehensive assessment of traditional epidemiological biases including confounding, selection, and information biases, as well as bias relating to how authors handle missing data and the choice of outcome (17). All eligible publications were included in the qualitative synthesis regardless of their assessed risk of bias. This was decided beforehand because of pre-existing knowledge of the literature and the known critical risk of confounding in retrospective cohort studies without control groups.

Statistical Analysis

We used a descriptive analytical approach to synthesize the incidence of bleeding associated with the use of therapeutic anticoagulation for VTE during pregnancy. Due to the known substantial heterogeneity between included publications in terms of bleeding definitions, it was decided that it would not be meaningful to meta-analyze the extracted data.

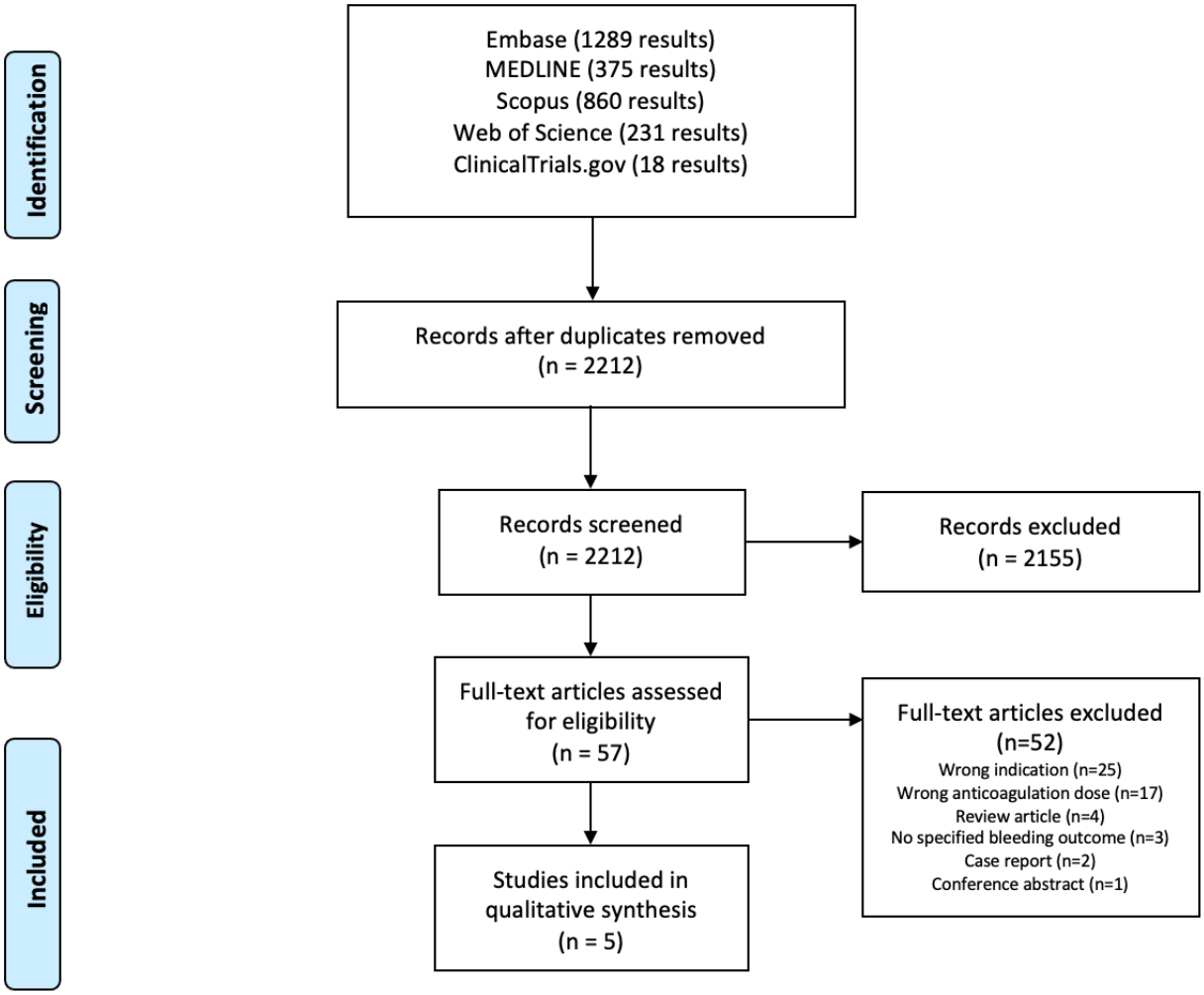
RESULTS

Search results

A total of 2773 articles were identified with our search, 2212 of which remained after duplicates were removed. 2155 publications were excluded following title and abstract screening, and 57 articles underwent full-text review. Articles were excluded if they described patients treated with an anticoagulant at a dose other than therapeutic (n=17), if the main indication for anticoagulation was other than VTE (n=25), or if the article had no specified bleeding outcome (n=3). Review articles (n=4), case reports (n=2), and a conference abstract (n=1) were also

excluded following full-text review. Five articles meeting all inclusion criteria were included in our systematic review (Figure 1).

Figure 1. Flow diagram of the systematic search used to identify studies performed on February 27, 2022



Study characteristics

The characteristics of included studies can be found in Table 1. Four retrospective cohort (8-10, 18) and one prospective cohort studies (19) were included, representing a total of 1487 participants (611 receiving therapeutic-dose anticoagulation and 876 controls). Therapeutic-dose

anticoagulation was administered with LMWH or unfractionated heparin. Two studies included control groups of pregnant women without acute VTE who were not receiving anticoagulation (8, 9), while the remaining studies had no control group (10, 18, 19). The bleeding definitions used in individual studies were variable. Two studies used the International Society on Thrombosis and Haemostasis (ISTH) major bleeding definition, which includes fatal bleeding and/or bleeding in a critical area or organ, and/or bleeding causing a fall in hemoglobin level of 20 g/L or leading to an intravenous transfusion of two or more units of whole blood or red cells (18, 19). One study used a composite endpoint of major hemorrhagic complication comprising bleeding requiring surgery, hospital readmission, admission to the intensive care unit, red blood cell transfusion or fluid resuscitation of 1 L or more of crystalloids for bleeding concerns (10). The two remaining studies used PPH as a bleeding endpoint, with one study using different bleeding thresholds according to the mode of delivery (i.e. PPH of 500 mL or more and severe PPH of 1000 mL or more for vaginal delivery, and a blood loss of 1000 mL or more for cesarean section (CS)) (8), while the other study defined PPH and severe PPH without differentiation by mode of delivery (9).

Table 1. Studies evaluating bleeding in pregnant women treated for acute VTE

Study	Year of publication	Study design	Population size (n)	Control group size (n)	Intervention	Bleeding definition	Bleeding estimate
Blanco-Molina et al. (19)	2007	Prospective cohort study	136	NA	LMWH	ISTH definition of major bleeding (20)	**Major bleeding**: 4/136 (2.9%).
Chan et al. (18)	2012	Retrospective cohort study	60	NA	Once or twice daily LMWH	ISTH definition of major bleeding (20)	**Major bleeding**: 3/60 (5.0%, 95% CI 1.0-14.0%). 6 total bleeding events (6/60, 10.0%).
Côté-Poirier et al. (10)	2020	Retrospective cohort study	232	NA	Therapeutic dose LWMH or IVH	Major hemorrhagic complication*	**Major hemorrhagic complication**: 9/149 (6.0%, 95% CI 2.8-11.1) for VD and 7/83 (8.4%, 95% CI 3.5-16.6) for CS.
Knol et al. (8)	2012	Retrospective cohort study	88	352	Therapeutic dose nadroparin (175 units/kg/day)	VD: PPH ≥ 500 mL, severe PPH ≥ 1000 mL CS: PPH ≥ 1000 mL	**PPH**: 30.0% vs. 18.0% in treatment vs. control group (OR 1.9, 95% CI 1.1-3.5) for VD and 12.0% vs. 4.0% in treatment vs. control group (OR 2.9, 95% CI 0.5-19.4) for CS. **Severe PPH**:5.6% vs. 5.0% (OR 1.1, 95% CI 0.4-3.6) for VD.
Roshani et al. (9)	2011	Retrospective	95	524	Weight-based therapeut	PPH > 500 mL, severe PPH > 1000 mL	**PPH**: 18.0% in treatment group vs. 22.0% in control group (RR 0.8, 95% CI 0.5-1.4).

		cohort study			ic dose LMWH as defined by manufacturer		**Severe PPH**: 6.0% in both groups (RR 1.2 95% CI 0.5-2.9)

Abbreviation: NA= non-available, LMWH =low-molecular-weight heparin, IVH = intravenous heparin, ISTH = International Society on Thrombosis and Haemostasis, CI = confidence interval, OR = odds ratio, ICU = intensive care unit, CS = cesarean delivery, VD = vaginal delivery, PPH = postpartum hemorrhage.

**Major hemorrhagic complication defined as significant bleeding that occurred after the resumption of therapeutic anticoagulation requiring surgery, hospital readmission, admission to the intensive care unit, red blood cells transfusion, or fluid resuscitation of 1L or more of crystalloid (prescribed specifically for a bleeding concern after therapeutic anticoagulation resumption, so not related to the immediate intrapartum and postpartum period).*

Quality Assessment

Based on ROBINS-I, the risk of bias of most included studies ranged from serious to critical (Appendix B). Retrospective cohort studies without control groups were evaluated as having critical risk of confounding due to the absence of controls (10, 18, 19). All studies were judged to have a serious risk of bias in the measurement of the outcome due to the subjective nature of the bleeding outcome measurement in the absence of a standardized assessment method, and the vulnerability to influence from knowledge of the intervention in the absence of blinding of outcome assessors.

Bleeding complications

Reported major bleeding events according to the ISTH definition of major bleeding ranged between 2.9 and 5.0% in women receiving therapeutic anticoagulation for an acute VTE during pregnancy (18, 19). When evaluating PPH, one study showed a higher risk of PPH in women receiving therapeutic anticoagulation when compared to controls undergoing vaginal delivery (30.0% vs. 18.0%, odds ratio (OR) 1.9, 95% confidence interval (CI) 1.1-3.5, p=0.029) (8), while another did not find a significant difference between the intervention and control groups (18.0% vs. 22.0%, relative risk (RR) for PPH 0.8, 95% CI 0.5-1.4) (9). In the study using the composite endpoint for major hemorrhagic complication, the outcome occurred in 6.0% (95% CI 3.5-16.6) of vaginal deliveries and 8.4% (95% CI 2.8-11.1) of cesarean deliveries (10).

DISCUSSION

Our systematic review describes published rates of bleeding with therapeutic-dose anticoagulation for VTE during pregnancy. Five observational cohort studies reported bleeding outcomes in this patient population and were evaluated as having serious to critical risk of bias, mainly due to the absence of a control group and subjective measurement of the bleeding outcome. We observed risk estimates of major bleeding as defined by the ISTH ranging between 2.9% and 5.0% and risk estimates of PPH between 12.0% and 30.0% associated with the use of therapeutic anticoagulation for VTE during pregnancy.

Whether the use of therapeutic-dose anticoagulation for the treatment of VTE in pregnancy increases the incidence of bleeding remains unclear. While some studies in our review included a comparator group and showed inconsistent results (8, 9), others only reported incidence estimates in the total study population exposed to anticoagulants (10, 18, 19). The reported incidence of postpartum bleeding is 5% to 15% in the general population according to the World Health Organization (WHO) estimates, although the global incidence and severity of bleeding events in pregnancy remains unknown (21). While some studies included in our review reported bleeding rates that were overall within a similar range as the general population (10, 18, 19), others reported bleeding rates beyond what would be expected (8, 9).

Several reasons may explain the reported variability in bleeding rates. Firstly, bleeding definitions are not standard across studies. This may indirectly be reflective of the lack of agreement across national guidelines regarding the definition of PPH. The Society of Obstetricians

and Gynecologists of Canada (SOGC) and the American College of Obstetricians and Gynecologists (ACOG) take into consideration the mode of delivery to define PPH as blood loss greater than 500 mL for vaginal deliveries and greater than 1000 mL for CS (22-24). The French College of Gynecologists and Obstetricians (FCOG) and the Royal Australian and New Zealand College of Obstetricians and Gynecologists (RANZCOG) define PPH as any blood loss greater than 500 mL and severe PPH as any blood loss greater than 1000 mL, irrespective of mode of delivery (25, 26). The Royal College of Obstetricians and Gynecologists (RCOG) in the United Kingdom further divides PPH into three categories: minor (500 mL to 1L), moderate (>1 to 2 L) and major (>2 L) bleeding events (27). In addition to varying bleeding thresholds and discrepancies in considering delivery mode, visual estimation of the amount of blood loss has been recognized as an unreliable measure of hemorrhagic events (21). Moreover, the measurement of the bleeding outcome is vulnerable to ascertainment bias associated to the knowledge of the intervention, therapeutic-dose anticoagulation, received by study participants.

Secondly, variability in bleeding rates may be due to differences in study populations. For example, aspirin use during pregnancy, which was only reported in two of the five included studies (8, 10), has been shown to be associated with an increased risk of postpartum bleeding (28). Maternal comorbidities and pregnancy complications including gestational diabetes, placenta previa or abruption, preeclampsia and eclampsia have been shown to increase the risk of postpartum hemorrhage (29, 30). These were not reported in included studies including control groups and may have differentially influenced bleeding rates (8, 9).

Thirdly, variability in peripartum clinical practices may have influenced rates of bleeding. Obstetric interventions, including the management of the third stage of labour, differ by center, and this variation may further explain the variability in reported bleeding outcomes. The highest rates of PPH were reported in two studies performed in the Netherlands. This may be partly explained by the fact that an active management of the third stage of delivery with prophylactic administration of oxytocics and early cord clamping is not routinely performed in these centres, although these interventions have been shown to reduce the amount of blood loss (8, 9). Anticoagulation may also not be routinely held antepartum, which may further increase peripartum blood loss (6). In addition, the time interval between delivery and resumption of anticoagulation in the postpartum period influences the risk of bleeding complications in patients treated with therapeutic anticoagulation for VTE, with shorter intervals leading to a higher risk of major hemorrhagic complication (10). Time interval for postpartum anticoagulation was not standardized across studies and was only reported in one included study (10).

The lack of standard bleeding definitions has affected the reliability of previously published bleeding estimates associated with the use of anticoagulation during pregnancy. A previous systematic review of anticoagulation for VTE during pregnancy including treatment with therapeutic and non-therapeutic doses of heparins reported an incidence of major PPH (defined by the RCOG as blood loss greater than 2 L) of 1.90% (95% CI 0.8-3.6%), with insufficient information provided on bleeding events in individual studies to apply a standardized bleeding classification. Given the limited information in some individual studies with regards to bleeding events, this rate should be interpreted cautiously (31). Another systematic review of pregnant patients with VTE treated with various doses of anticoagulation compared to controls receiving

either thromboprophylaxis or no anticoagulation reported no significant difference in the rate of antepartum bleeding events between the two groups (OR 1.08, 95% CI 0.84-1.40) (14). Our review contrasts the existing literature by reporting a wide range of bleeding events in patients receiving therapeutic-dose anticoagulation for VTE. It also complements previous reports by highlighting the urgent need for standardized bleeding definitions.

Our systematic review has limitations. First, the observational nature of the included studies with small numbers of patients carries an inherent risk of bias with regards to population selection and measure of outcome. Second, the lack of standardization in bleeding definitions precluded a meta-analysis of reported bleeding outcomes. The ACOG's reVITALize program has put forward a definition of PPH that includes cumulative blood loss regardless of route of delivery and signs or symptoms of hypovolemia which should alert clinicians to consequences of blood loss (32). Recently, the ISTH Scientific and Standardization Committee on Control of Anticoagulation has proposed a standardized classification of antepartum and postpartum bleeding events which classifies bleeding severity according to therapeutic interventions or consequence of blood loss rather than the bleeding event itself (21). Variable definitions of bleeding outcomes in studies evaluating anticoagulation use in pregnancy, whether prophylactic or other doses, is recognized by the committee. They propose uniform definitions of antepartum and postpartum bleeding events during pregnancy (21). These tools will undoubtedly help the standardization of bleeding severity in pregnant women receiving anticoagulation and facilitate future research. Moreover, the ongoing PREP & GO study will prospectively evaluate intrapartum and postpartum bleeding using standardized bleeding definitions for women on prophylactic and therapeutic doses of anticoagulation for VTE-related indications. This will help inform decisions on optimal

anticoagulation management and identify future research priorities for this patient population (33). Third, the lack of information and adjustment with regards to confounders including maternal comorbidities, co-medication, and management of the third stage of labour may have further influenced the risk of bleeding associated with the use of therapeutic anticoagulation for VTE in pregnancy. Lastly, other patient-important outcomes that may impact life such as minor bleeding, wound complications, and access to epidural anesthesia were not systematically evaluated (34).

CONCLUSION

Among women who received therapeutic anticoagulation for VTE during pregnancy, reported bleeding risks are variable. The available observational studies do not provide reliable bleeding estimates or inform clinicians as to whether the risk of clinically significant blood loss is increased with the use of anticoagulation compared to non-anticoagulated patients. The ability to make definite inference is limited by the observational nature of studies, the small number of patients and the heterogeneity of bleeding definitions. Larger scale studies with standardized bleeding outcomes are required to evaluate the bleeding risk associated with therapeutic anticoagulation to optimize the care of this patient population.

REFERENCES

1. Marik PE, Plante LA. Venous Thromboembolic Disease and Pregnancy. New England Journal of Medicine. 2008;359(19):2025-33.
2. Bailly J, Jacobson BF, Louw S. Safety and efficacy of adjusted-dose enoxaparin in pregnant patients with increased risk for venous thromboembolic disease. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2019;145(1):70-5.
3. James AH. Venous Thromboembolism in Pregnancy. Arteriosclerosis, thrombosis, and vascular biology. 2009;29(3):326-31.
4. Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018;2(22):3317-59.
5. Chan WS, Rey E, Kent NE, Chan WS, Kent NE, Rey E, et al. Venous thromboembolism and antithrombotic therapy in pregnancy. J Obstet Gynaecol Can. 2014;36(6):527-53.
6. Middeldorp S, Ganzevoort W. HEMATOLOGIC COMPLICATIONS IN PREGNANCY How I treat venous thromboembolism in pregnancy. Blood. 2020;136(19):2133-42.
7. Rath W, von Tempelhoff GF, Tsikouras P. How to Reduce Maternal Mortality From Venous Thromboembolism. Clin Appl Thromb Hemost. 2018;24(9_suppl):6s-7s.
8. Knol HM, Schultinge L, Veeger NJGM, Kluin-Nelemans HC, Erwich JJHM, Meijer K. The risk of postpartum hemorrhage in women using high dose of low-molecular-weight heparins during pregnancy. Thrombosis Research. 2012;130(3):334-8.
9. Roshani S, Cohn DM, Stehouwer AC, Wolf H, Van Der Post JAM, Büller HR, et al. Incidence of postpartum haemorrhage in women receiving therapeutic doses of low-molecular-weight heparin: Results of a retrospective cohort study. BMJ Open. 2011;1(2).
10. Cote-Poirier G, Bettache N, Cote AM, Mahone M, Morin F, Cumyn A, et al. Evaluation of Complications in Postpartum Women Receiving Therapeutic Anticoagulation. Obstetrics and Gynecology. 2020;136(2):394-401.
11. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):e323-33.
12. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005;106(2):401-7.
13. Sirico A, Saccone G, Maruotti GM, Grandone E, Sarno L, Berghella V, et al. Low molecular weight heparin use during pregnancy and risk of postpartum hemorrhage: a systematic review and meta-analysis. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet. 2019;32(11):1893-900.
14. Chen GC, Gao H, Zhang L, Tong T. Evaluation of therapeutic efficacy of anticoagulant drugs for patients with venous thromboembolism during pregnancy: A systematic review and meta-analysis. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2019;238:7-11.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ (Clinical research ed). 2009;339:b2700.

16. Simard C, Gerstein L, Cafaro T, Malhamé I, Douros A, Filion KB, Tagalakis V. Bleeding Complications in Women with Venous Thromboembolism during Pregnancy: A Systematic Review of the Literature. PROSPERO: International prospective register of systematic reviews. 2021 [Available from: http://www.crd.york.ac.uk/prospero/display_record.php?RecordID=276771.
17. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ (Clinical research ed). 2016;355:i4919.
18. Chan N, Merriman E, Hyder S, Woulfe T, Tran H, Chunilal S. How do we manage venous thromboembolism in pregnancy? A retrospective review of the practice of diagnosing and managing pregnancy-related venous thromboembolism at two major hospitals in Australia and New Zealand. Internal Medicine Journal. 2012;42(10):1104-12.
19. Blanco-Molina Á, Rota L, Di Micco P, Brenner B, Trujillo-Santos J, Ruiz-Gamietea A, et al. Venous thromboembolism during pregnancy, postpartum or during contraceptive use: Findings from the RIETE Registry. Thrombosis and Haemostasis. 2010;103(2):306-11.
20. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13(11):2119-26.
21. Tardy B, Chalayer E, Kamphuisen PW, Ainle FN, Verhamme P, Varlet MN, et al. Definition of bleeding events in studies evaluating prophylactic antithrombotic therapy in pregnant women: A systematic review and a proposal from the ISTH SSC. Journal of Thrombosis and Haemostasis. 2019;17(11):1979-88.
22. Practice Bulletin No. 183: Postpartum Hemorrhage. Obstet Gynecol. 2017;130(4):e168-e86.
23. Lalonde A. Prevention and treatment of postpartum hemorrhage in low-resource settings. Int J Gynaecol Obstet. 2012;117(2):108-18.
24. Leduc D, Senikas V, Lalonde AB. No. 235-Active Management of the Third Stage of Labour: Prevention and Treatment of Postpartum Hemorrhage. Journal of Obstetrics and Gynaecology Canada. 2018;40(12):e841-e55.
25. Sentilhes L, Vayssière C, Deneux-Tharaux C, Aya AG, Bayoumeu F, Bonnet MP, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). European journal of obstetrics, gynecology, and reproductive biology. 2016;198:12-21.
26. Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Management of postpartum hemorrhage. March 2011. [Available from: http://www.ranzcog.edu.au/collegestatements-guidelines.html.
27. Royal College of Obstetrician and Gynaecologists. Postpartum hemorrhage: prevention and management. April 2011. [Available from: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg52/.
28. Hastie R, Tong S, Wikström AK, Sandström A, Hesselman S, Bergman L. Aspirin use during pregnancy and the risk of bleeding complications: a Swedish population-based cohort study. American journal of obstetrics and gynecology. 2021;224(1):95.e1-.e12.

29. Muche AA, Olayemi OO, Gete YK. Effects of gestational diabetes mellitus on risk of adverse maternal outcomes: a prospective cohort study in Northwest Ethiopia. BMC pregnancy and childbirth. 2020;20(1):73.
30. Kramer MS, Berg C, Abenhaim H, Dahhou M, Rouleau J, Mehrabadi A, et al. Incidence, risk factors, and temporal trends in severe postpartum hemorrhage. American journal of obstetrics and gynecology. 2013;209(5):449.e1-7.
31. Romualdi E, Dentali F, Rancan E, Squizzato A, Steidl L, Middeldorp S, et al. Anticoagulant therapy for venous thromboembolism during pregnancy: A systematic review and a meta-analysis of the literature. Journal of Thrombosis and Haemostasis. 2013;11(2):270-81.
32. Menard MK, Main EK, Currigan SM. Executive summary of the reVITALize initiative: standardizing obstetric data definitions. Obstetrics and gynecology. 2014;124(1):150-3.
33. International Network of VENous Thromboembolism Clinical Research Networks (INVENT). A prospective cohort study evaluating peripartum anticoagulation management among pregnant women with VTE and its impact on patient outcomes (PREP & GO). [Available from: https://www.invent-vte.com/studies/study/~850-prep---go.
34. Kealy MA, Small RE, Liamputtong P. Recovery after caesarean birth: a qualitative study of women's accounts in Victoria, Australia. BMC pregnancy and childbirth. 2010;10(1):47.

APPENDIX A. Search strategy used in MEDLINE

Postpartum hemorrhage.mp. or Postpartum Hemorrhage/ OR ((postpartum or post partum or antepartum or ante partum or peripartum or peri partum).mp. AND (hemorrhag* or haemorrhag* or bleeding.mp.) AND Heparin, Low-Molecular-Weight/ OR low molecular weight heparin.mp. OR Heparin/ OR heparin.mp.

APPENDIX B. Quality Assessment of Included Studies

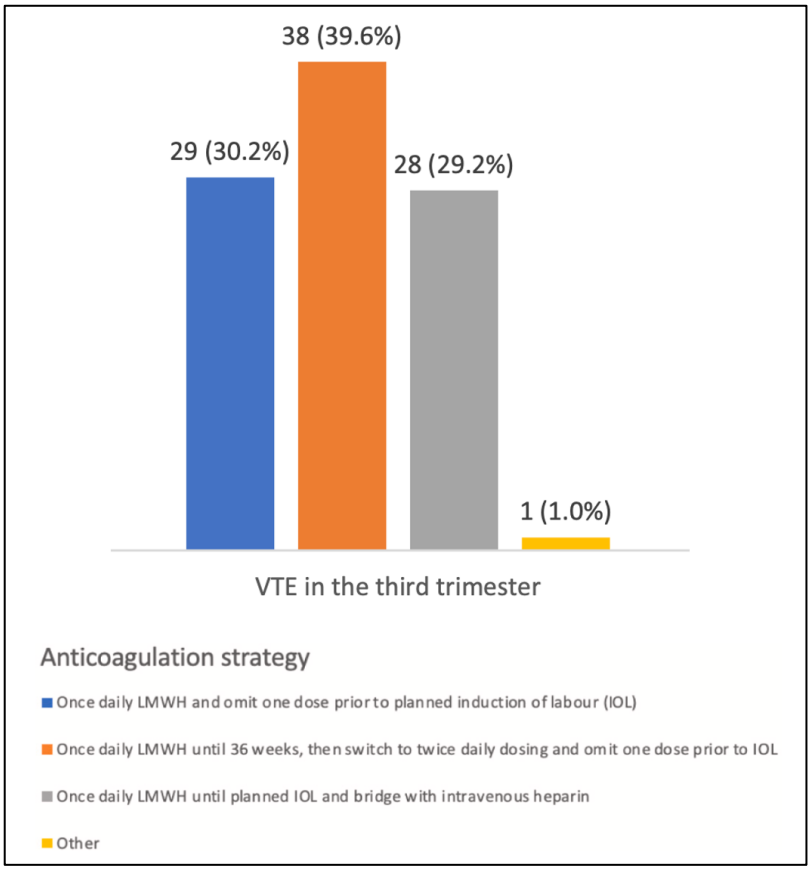
	Bias Domain								
Study	**Outcome**	**Confounding**	**Selection of the participants in the study**	**Classification of intervention**	**Deviation from intended interventions**	**Missing data**	**Measurement of outcomes**	**Reported results**	**Overall**
Blanco-Molina et al. (19)	Major bleeding	Critical	Moderate	Low	Low	Low	Serious	Low	Critical
Chan et al. (18)	Major bleeding	Critical	Moderate	Low	NI	Low	Serious	Low	Critical
Côté-Poirier et al. (10)	Major hemorrhagic complication	Critical	Moderate	Low	NI	Moderate	Serious	Low	Critical
Knol et al. (8)	Postpartum hemorrhage	Serious	Moderate	Low	Low	Moderate	Serious	Low	Serious
Roshani et al. (9)	Postpartum hemorrhage	Serious	Moderate	Low	Low	Moderate	Serious	Low	Serious

Abbreviation: NI: not included

CHAPTER 3: TRANSITION

The systematic review of the literature highlighted the need for population-based estimates of bleeding in women treated with LMWH for VTE during pregnancy. To better understand the current clinical practice of healthcare professionals as well as their perception of the bleeding risk associated with therapeutic LMWH during pregnancy, we conducted an international survey evaluating the practice of healthcare providers caring for pregnant women. The objective of this survey was to highlight practice variation and inconsistent perception with regards to bleeding, to further establish the need for population-based bleeding estimates. In the survey results of 96 international respondents, we found substantial variations in dosing strategies and peripartum management of anticoagulation (8). When presented a clinical vignette describing a patient with a stable PE in the early third trimester, 30.2% of respondents opted to keep once daily therapeutic-dose LMWH, 39.6% opted to switch to twice daily dosing at 36 weeks' gestation and 29.2% chose to admit the patient for bridging with intravenous heparin peripartum (Figure 8) (8). This further clarified the need for comparing once vs. twice daily dosing of therapeutic-dose LMWH around delivery with regards to the risk of bleeding. Moreover, when questioned about their perceived risk of bleeding associated with the use of therapeutic anticoagulation, there was no clear consensus as to whether therapeutic anticoagulation increases the risk of clinically relevant non-major bleeding, as defined by the ISTH (Figure 9) (35). These variations are likely driven by the lack of consensus with regards to bleeding definitions, both in clinical practice and in the literature, and the poor quality of available studies evaluating bleeding in these patients, as highlighted by our systematic review.

Figure 8. Peripartum anticoagulation management of a venous thromboembolism in the third trimester (8)



Abbreviations: LMWH = low-molecular-weight heparin, VTE = venous thromboembolism. Figure adapted from Simard et al. Thrombosis Research, 2021.

Figure 9. Physician perception of bleeding risk in women treated with therapeutic anticoagulation for venous thromboembolism during pregnancy (8)

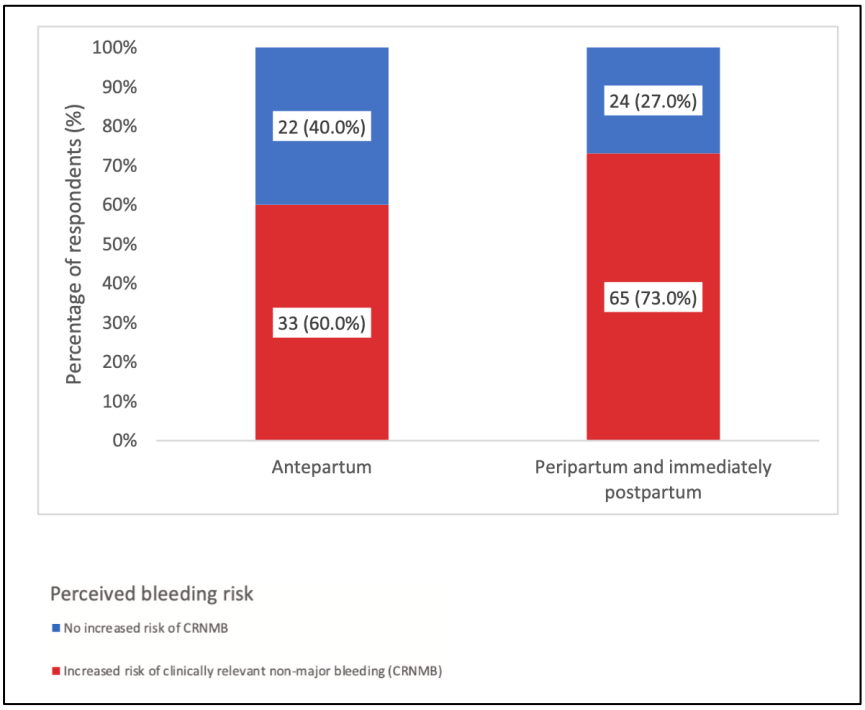


Figure from Simard et al. Thrombosis Research, 2021.

Canadian utilization data for anticoagulant medications in the general population has shown that over 50% of LMWH prescriptions dispensed are for dalteparin (65). Preliminary exploration of utilization data from the province of Québec shows that dalteparin is also the preferred LMWH for the treatment of VTE, with over 70% of pregnant women with VTE receiving dalteparin. Since dalteparin is the preferred anticoagulant in pregnancy, understanding whether this LMWH type confers a benefit regarding bleeding complications needs to be determined.

CHAPTER 4: ORIGINAL RESEARCH

4.1 Preface to second manuscript

Based on the systematic review of the literature which showed a wide range of bleeding estimates between 2.9% and 30.0% using variable bleeding definitions across studies and our survey of clinical practice which showed practice variation with regards to anticoagulant management, we recognized the need for population-derived estimates to evaluate the association between the use of LMWH for the treatment of VTE during pregnancy and the risk of bleeding. We performed a population-based cohort study evaluating the risk of bleeding associated with the use of the most commonly used LMWH, dalteparin, compared to enoxaparin or tinzaparin. We explored the difference in the incidence of bleeding, including antepartum and postpartum bleeding events. Given practice variation with regards to LMWH dosing (daily vs. twice daily), we compared the incidence of bleeding between these two dosing strategies. We discuss our findings, as well as the limitations of the results in the discussion section of the manuscript. Details of the methodology and the algorithm used to identify the study population are also presented in a supplement following the manuscript.

4.2 Cohort study manuscript

The Risk of Bleeding in Pregnant Women with Acute Venous Thromboembolism Treated with Anticoagulants

Camille Simard[1-3], Isabelle Malhamé[2,4,5], Christopher Filliter[6], Antonios Douros[2,6,7], Kristian B. Filion[1,2,6], Haim Abenhaim[8,9], Vicky Tagalakis[2,3,6] for the Canadian Venous Thromboembolism Research Network (CanVECTOR) Network

[1]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada [2]Department of Medicine, McGill University, Montreal, Canada [3]Division of General Internal Medicine, Jewish General Hospital, Montreal, QC, Canada [4]Division of General Internal Medicine, McGill University Health Centre, Montreal, QC, Canada [5]Research Institute of the McGill University Health Centre, McGill University Health Centre, Montreal, QC, Canada [6]Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada [7]Institute of Clinical Pharmacology and Toxicology, Charité, Universitätsmedizin Berlin, Berlin, Germany [8]Division of Obstetrics and Gynecology, Jewish General Hospital, Montreal, QC, Canada [9]Centre for Clinical Epidemiology and Community Studies, Jewish General Hospital, Montreal, QC, Canada

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Corresponding author:
Dr. Camille Simard
Division of General Internal Medicine, Jewish General Hospital
3755 Côte-Sainte-Catherine, Rm B-304.29
Montreal, Québec, Canada
H3T 1E2
Tel: 1-514-340-8222 ext. 27015
Email: camille.simard@mcgill.ca

Abstract

INTRODUCTION

Pregnant women diagnosed with venous thromboembolism (VTE) are usually treated with low-molecular-weight heparin (LMWH). Dalteparin is the most prescribed LMWH in Canada. LMWHs differ in their pharmacodynamic and pharmacokinetic properties, which may affect the risk of bleeding associated with their use. Moreover, LMWH may be given in once vs. twice daily dosing, which may affect peripartum bleeding risks. We aimed to better characterize bleeding events in women with LMWH by estimating the risk of bleeding with LMWH, comparing the risk of bleeding between the use of dalteparin vs. enoxaparin or tinzaparin, and comparing the risk with once vs. twice daily peripartum dosing among patients treated for VTE during pregnancy.

MATERIALS AND METHODS

We conducted a retrospective cohort study using data from the linked electronic administrative healthcare databases of the province of Québec, Canada. We followed a cohort of pregnant women diagnosed with VTE during pregnancy and treated with dalteparin, enoxaparin, or tinzaparin until an inpatient diagnosis of bleeding or censoring due to discontinuation of LMWH use, cessation of medication coverage eligibility, death, or the end of the study period (December 31, 2015). Major bleeding was defined as a hospitalization for bleeding or bleeding-related death within the study period.

RESULTS

The study cohort comprised 259 women treated with LMWH for a VTE during pregnancy. 188 (72.6%) women received dalteparin, and 71 women received enoxaparin or tinzaparin (27.4%). A total of 20 patients (7.7%) experienced bleeding during hospitalization during the study period. The results regarding a potential difference in the risk of bleeding between dalteparin and enoxaparin or tinzaparin were limited by the uncertainty around the estimates; however, the risk estimate was close to the null (hazard ratio (HR) 0.9, 95% confidence interval (CI) 0.2-2.5). A similar pattern was observed when comparing treatment with once vs. twice daily LMWH (HR 0.8, 95% CI 0.2-2.9).

CONCLUSION

We provide a population-derived estimate of bleeding in patients treated with LMWH for a VTE during pregnancy. Larger epidemiologic studies and randomized trials are needed to better address the factors related to LMWH management in pregnant women to optimize the care of this patient population.

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of maternal mortality in high-income countries (1). Pregnancy represents a hypercoagulable state resulting from the hormonally induced decreased venous capacitance, decreased venous return, increased concentrations of coagulation factors and peripartum vascular injury (2). Women are usually treated with subcutaneous weight-adjusted low-molecular-weight heparin (LMWH) for acute VTE during pregnancy. Anticoagulation is recommended for a minimum of three months, with LMWH usually continued until at least six weeks postpartum (3, 4).

Individual LMWHs, including dalteparin, enoxaparin and tinzaparin, are considered as having similar anticoagulant properties (5). However, in Canada, over 50% of prescriptions dispensed LMWHs are for dalteparin (6). Whether dalteparin is associated with safety benefits is not known. Moreover, LMWHs differ in their pharmacodynamic and pharmacokinetic properties, which may impact anticoagulant-related bleeding risks (5). In the non-pregnant population, evidence pertaining to the risk of bleeding with different LMWHs has been contradictory: while some studies demonstrated no difference with regards to bleeding complications between enoxaparin compared to dalteparin or tinzaparin (7, 8), a large randomized trial has shown a lower rate of major bleeding with fondaparinux compared with enoxaparin in patients with myocardial infarction (9). Since dalteparin is the preferred LMWH, and individual LMWHs may have different safety profiles, determining whether dalteparin is associated with a lower risk of bleeding is important.

Physiological changes in pregnancy, which include increased volume of distribution caused by increases in body weight and glomerular filtration rate may differentially affect pharmacodynamic characteristics of individual LMWHs (10). Moreover, LMWH can be administered once or twice daily during pregnancy (3, 4). Clinicians often opt to treat with once daily LMWH for ease of administration, with some transitioning to twice daily dosing around delivery because of a perceived lower bleeding risk (11). Whether twice daily dosing reduces the risk of bleeding around delivery is not well understood (4).

Using a defined study population, we sought to characterize the risk of bleeding in patients treated with LMWHs for VTE in pregnancy. The primary objectives were (1) to report a population-based estimate of major bleeding in this population and (2) to compare the risk of major bleeding among pregnant women with acute VTE treated with dalteparin vs. enoxaparin or tinzaparin. Secondary objectives were (1) to compare the risk of antepartum and postpartum bleeding between dalteparin vs. enoxaparin or tinzaparin and (2) to compare the risk of bleeding events with once daily dosing vs twice daily dosing of any LMWH.

Methods

Data source

We conducted a retrospective, population-based cohort study using data extracted from the linked electronic administrative healthcare databases in the province of Québec, Canada including the Régie de l'assurance maladie du Québec (RAMQ), the Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MEDÉCHO), and the Institut de la

statistique du Québec (ISQ). The RAMQ database contains information about patient demographics, outpatient diagnoses codes using the International Classification of Diseases (ICD), 9th Revision (ICD-9) or enhanced version of ICD 10th revision for Canada (ICD-10-CA), outpatient procedures and outpatient prescriptions. The quality of RAMQ data has previously been validated and shown to be highly specific for different conditions, diagnoses, and drug prescriptions (12, 13). The MEDÉCHO database includes records of all hospitalizations in Québec with date and type of admission and discharge, inpatient diagnoses, and inpatient procedures. The ISQ database contains vital statistics including the date and cause of death. The study protocol was approved by the Research Ethics Board of the Jewish General Hospital in Montreal, Québec (project number 2022-3111).

Study population

The source population comprised all women aged 18-45 years with an incident VTE during pregnancy among Québec residents eligible for RAMQ medication coverage with a diagnosis of incident VTE between January 1, 1998, and December 31, 2015. Included individuals were continuously insured by the Public Prescription Drug Insurance Plan of the RAMQ for at least six months prior to incident VTE. Women with a prescription for LMWH within a year of incident VTE were excluded from the cohort. Information on length of gestation (in weeks), available in the MEDÉCHO database, was used to identify women who were pregnant at the time of the incident VTE. When that variable was not available, a previously validated algorithm was used to estimate the date of conception (14-16).

From the source population, we included women who initiated LMWH within 15 days of incident VTE to avoid selection bias. The date of study cohort entry was 15 days after the date of incident VTE. To further reduce the risk of selection bias, we excluded women whose follow-up ended before or on date of cohort entry, either because they switched exposure group (from one LMWH type to another type), because of end of registration, or study end date. All women were followed from cohort entry until the earliest of the following: (1) occurrence of major bleeding or bleeding-related death (defined below), (2) discontinuation of LMWH defined as a gap of at least 30 days after the end of a prescription and the beginning of another prescription, (3) a prescription for a non-LMWH anticoagulant (vitamin K antagonist or direct oral anticoagulant), (4) a prescription for a different LMWH anticoagulant (intra-class switch), (5) end of the registration with the Public Prescription Drug Insurance Plan of the RAMQ or (6) study end date on December 31, 2015.

Exposure definition

Exposure was defined as a prescription for LMWH within 15 days of incident VTE. Patients were classified into two mutually-exclusive categories; (1) dalteparin users; (2) enoxaparin or tinzaparin users. LMWH was defined using an on-treatment approach that assessed the risk of major bleeding while using LMWH. Patients were considered continuously exposed to LMWH when prescription durations were overlapping each other while allowing a 30-day grace period in the event of a non-overlapping prescription.

To identify once daily vs. twice daily LMWH prescriptions, cohort entry was shifted for 15 days following incident VTE to 30 days following incident VTE. Prescriptions for LMWH between day 15 and day 30 were used to categorize individuals into once vs. twice daily dosing. we assesssed the exposure during the first 15 days following cohort entry. We assessed the exposure at a fixed-point following cohort entry to avoid selection bias. When the total dispensed dose of LMWH exceeded 15 doses in 15 days, LMWH was considered as prescribed twice daily. Conversely, if the total dispensed dose of LMWH was less than 15 doses in that period, LMWH was considered to be prescribed once daily.

Outcome definition

The primary outcome was major bleeding, defined as (i) an inpatient diagnostic code for bleeding (anywhere in the hospitalization record; complete list of diagnostic codes in Appendix A) or (ii) death due to bleeding (Appendix A). Major bleeding included both pregnancy-related and non-pregnancy related bleeding events (Appendix A) (17, 18). Secondary outcomes included antepartum and peripartum bleeding and all-cause mortality. Obstetric bleeding was classified as being antepartum if it occurred prior to delivery hospitalization, or postpartum if it occurred after delivery until 6 weeks postpartum. The MEDÉCHO and ISQ databases were used to ascertain maternal mortality. All death events were assigned the 15th of the respective month as date of death, as the ISQ database contains month and year but not exact date of death due to data protection regulations.

Covariate selection

A directed acyclic graph was used to depict the causal relationship between variables included in the conceptual framework to identify confounding variables using subject matter expertise (Appendix B) (19). Covariates were identified in the year prior to pregnancy and were defined using relevant diagnostic codes (Appendix C). Maternal comorbidities were defined using an assessment window that included the duration of pregnancy as well as 1 year prior to pregnancy. To estimate the direct effect of LMWH choice on bleeding events, chronic kidney disease and obesity were identified as potential confounders.

Statistical analyses

We calculated crude incidence rates for the primary and secondary outcomes using 95% confidence intervals (CIs). We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs of the study outcomes associated with the use of dalteparin compared to the use of enoxaparin or tinzaparin, bleeding outcomes associated with once compared to twice daily dosing of LMWH, and all-cause mortality in women treated with LMWHs. There was insufficient patients to adjust for previously identified confounders. We performed four sensitivity analyses. First, to better estimate the effect of LMWH dosing (daily vs. twice daily) at the time of delivery, we performed an exploratory sensitivity analysis that restricted to incident VTE occurring at 30 weeks of gestation or later. Second, because we assumed that pregnant patients treated with LMWH for an acute VTE have an overall good adherence to treatment, we used a 15-day grace period between non-overlapping successive prescriptions to assess for possible exposure misclassification. Third, we used the 1st day of the month as date of death in

the ISQ database to assess for mortality, to assess for possible misclassification of the outcome for mortality. Finally, we performed an intention-to-treat analysis to assess the potential impact of informative censoring due to the as-treated exposure definition. All analyses were performed using SAS (version 9.4).

Results

A total of 259 pregnant women with a diagnosis of VTE during pregnancy initiated a prescription for LMWH within 15 days of incident VTE (Figure 1). Of these, 188 (72.6%) received a prescription for dalteparin and 71 (27.4%) received a prescription for either enoxaparin or tinzaparin. Table 1 shows patient characteristics at study cohort entry stratified by LMWH group. The mean age was 29 years (standard deviation (SD) 6.1). A total of 78.0% of patients had a diagnosis of deep vein thrombosis (DVT), 22.0% had a diagnosis of PE. Six (2.3%) patients had chronic hypertension and 8 (3.9%) had a diagnosis of diabetes mellitus. The utilization of enoxaparin and tinzaparin increased in recent years. Women treated with enoxaparin or tinzaparin were more likely to be treated for a PE rather than a DVT and had a higher proportion of chronic pulmonary disease.

Overall, 20 patients (7.7%) had a major bleeding event, 15 (5.8%) in the dalteparin group and 5 (1.9%) in the enoxaparin or tinzaparin group. Bleeding events occurred up to 34 days postpartum. The incidence rate of major bleeding was 300.4 per 1000 person-years in the dalteparin group (95% CI 168.1-495.5) and 345.1 per 1000 person-years in the enoxaparin or tinzaparin group (95% CI 112.1-805.4). Compared with the uses of enoxaparin or tinzaparin, the crude HR for bleeding with dalteparin was 0.9 (95% CI 0.3-2.5) (Table 2). Since no participant

had kidney disease in the dalteparin group and no participant had obesity in the enoxaparin or tinzaparin group, our model could not be adjusted for these comorbidities. In addition, there were no difference in antepartum or postpartum bleeding events in both groups (Table 2). There were no deaths. Once daily dosing of LMWH did not appear to be associated with a higher bleeding incidence compared to twice daily dosing LWMH (Table 2). The sensitivity analyses performed yielded findings that were consistent with those of the primary analysis (Appendices D and E).

Figure 1. Flowchart of the study cohort

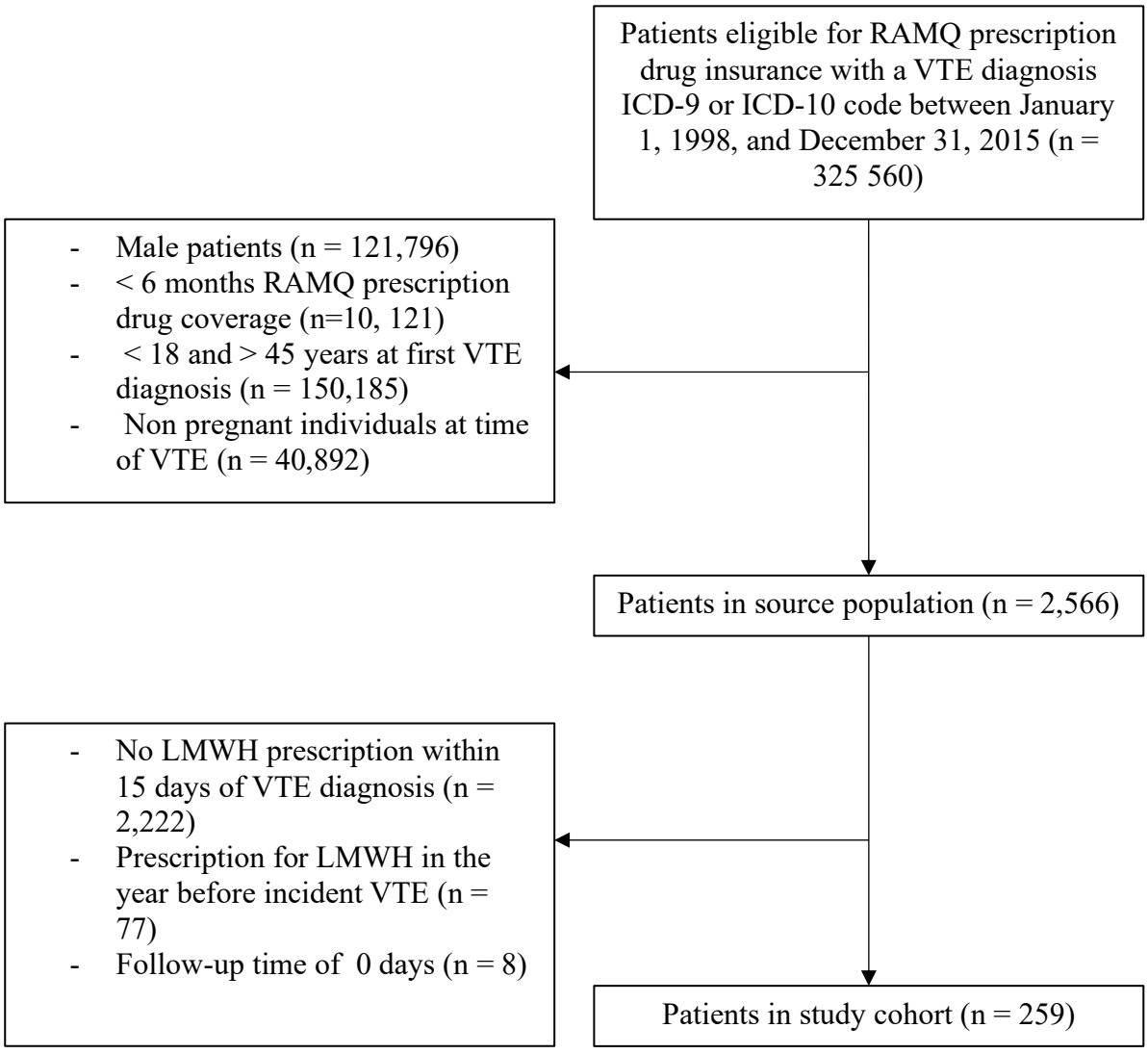


Table 1. Characteristics of pregnant patients treated with therapeutic dose dalteparin compared to enoxaparin or tinzaparin for venous thromboembolism

Characteristic	Dalteparin	Enoxaparin or tinzaparin
	n or mean (% or SD)	n or mean (% or SD)
	188 (72.6)	71 (27.4)
VTE characteristic		
Year of VTE		
1998-2003	62 (33.00)	16 (22.5)
2004-2009	52 (27.7)	19 (26.8)
2010-2015	74 (39.4)	36 (50.7)
Type of VTE		
Deep vein thrombosis	152 (80.9)	50 (70.4)
Pulmonary embolism	36 (19.1)	21 (29.6)
Pregnancy characteristic		
Multiple gestation	8 (4.3)	0 (0)
Prolonged labour	*	*
Placenta previa	*	0 (0)
Previous cesarian delivery	8 (4.3)	0 (0)
Maternal characteristic		
Age	29.8 (6.1)	28.4 (6.3)
Gestational age	20.5 (10.4)	22.2 (11.5)
Chronic hypertension	5 (2.7)	*
Gestational hypertension	0 (0)	0 (0)
Preeclampsia/eclampsia	*	0 (0)
Chronic kidney disease	0 (0)	*
Heart disease (any)	*	*
Diabetes mellitus	8 (4.3)	*
Hypothyroidism	*	*
Anemia	*	0 (0)
Systemic lupus erythematosus	0 (0)	0 (0)
Tobacco smoking	*	*
Drug use disorder	*	0 (0)
Chronic pulmonary disease	8 (4.3)	7 (9.9)
Malignancy (any)	*	*
Obesity	*	0 (0)

Abbreviations: %: percentage of patients; n: number of patients; SD: standard deviation; VTE: venous thromboembolism

**Any cells with less than 5 patients were suppressed as per RAMQ privacy policy.*

Table 2. Incidence of bleeding and death in patients treated with LMWH for VTE during pregnancy

	Patients (n)	Events (n)	Person-years	Incidence rate (95% CI) **	Crude HR (95% CI)
Major bleeding					
Any LMWH	259	20	64.4	310.5 (189.6-479.5)	NA
Dalteparin vs. enoxaparin/tinzaparin					
Dalteparin	188	15	49.9	300.4 (168.1-495.5)	0.9 (0.2-2.5)
Enoxaparin/tinzaparin	71	5	14.5	345.1 (112.1-805.4)	1 (Ref)
Antepartum obstetric bleeding					
Dalteparin	188	5	50.9	98.1 (31.9-229.0)	NA
Enoxaparin/tinzaparin	71	0	14.7	0.0 (0.0)	1.0 (Ref)
Postpartum obstetric bleeding					
Dalteparin	188	9	50.8	177.3 (81.1-336.6)	0.7 (0.2-2.2)
Enoxaparin/tinzaparin	71	*	*	275.2 (75.0-704.5)	1.0 (Ref)
All-cause related mortality					
Dalteparin	188	0	51.7	0.0 (0.0)	NA
Enoxaparin/tinzaparin	71	0	14.7	0.0 (0.0)	1.0 (Ref)

**Any cells with less than 5 patients were suppressed as per RAMQ privacy policy.*
***Per 1000 person-years*
Abbreviations: CI: confidence interval, HR: hazard ratio, NA: not available, n: number of patients, Ref: reference.

Table 3. Incidence of bleeding in patients treated with once daily vs. twice daily LMWH for VTE during pregnancy

	Patients (n)	Events (n)	Person-years	Incidence rate (95% CI) **	Crude HR (95% CI)
Once daily LMWH	153	7	32.0	219.0 (88.0-451.2)	1.0 (Ref)
Twice daily LMWH	70	*	*	177.3 (48.3-453.9)	0.8 (0.2-2.9)

**Any cells with less than 5 patients were suppressed as per RAMQ privacy policy.*
***Per 1000 person-years*
Abbreviations: CI: confidence interval, HR: hazard ratio, n: number of patients, Ref: reference.

Discussion

We report the risk of bleeding associated with anticoagulant use in a population-based cohort of women with incident VTE in pregnancy. Overall, 7.7% of women experienced a bleeding event, representing an incidence of 310.5 per 1000 person-years. Dalteparin was the most dispensed LMWH. We did not observe a significant difference in bleeding in women treated with dalteparin vs. enoxaparin or tinzaparin for a VTE during pregnancy. Moreover, we did not detect a difference in bleeding between once vs. twice daily LMWH dosing.

We found 20 (7.7%) major bleeding events in our population. A recent systematic review of the literature described risks of major bleeding, as defined by the individual study, between 2.9% and 30.0% (20). In the included studies, bleeding was defined as postpartum hemorrhage, or a composite outcome of bleeding which included variables such as bleeding in a critical organ, drop in hemoglobin level >20 g/L, need for transfer to the intensive care unit, or blood product transfusion (21, 22). Our population-based cohort study provides an estimate of hospitalizations with bleeding, both antepartum and postpartum, an outcome that is relevant to patients and healthcare providers. Moreover, while dalteparin is the most commonly used LMWH in Canada, it does not appear to confer a benefit pertaining to bleeding complications in pregnancy (6). Our conclusions are limited by the uncertainty around the bleeding incidences with wide confidence intervals and should be considered to be hypothesis generating.

While pharmacological properties including mean molecular weight, elimination half-life and anti-Xa activity differ between these three LMWH agents (23), this does not appear to

translate into clinically different safety profiles in this patient population. Moreover, an international survey assessing the management of therapeutic anticoagulation in pregnant women with VTE showed that a significant proportion of healthcare providers opt to transition to twice daily LMWH dosing prior to induction of labour (11). This is done because of a perceived lower risk of bleeding around delivery with twice daily LMWH dosing (11). However, our findings suggest that this practice is not associated with a decreased risk of bleeding while being cumbersome for patients.

There are some potential limitations to the present study. First, a significant proportion of the source population was excluded because patients with an ICD code for VTE did not have a prescription for LMWH, leaving only 259 women in study population. This reflects an inherent limitation of population-based data, where patients being evaluated for the presence or absence of a pathology, in this case VTE, are identified with ICD codes. We hypothesize that these patients were evaluated for VTE and were found not to have a thrombosis, which lead to the absence of a LMWH prescription, or were diagnosed with thrombotic event that may not require LMWH therapy, such as below-knee DVT or superficial vein thrombosis (SVT). Second, women who did not deliver in a hospital setting and women who are not covered by a RAMQ drug plan were not captured in our study. Given that women with an acute VTE are considered to have high risk pregnancies, we expect that the majority would be treated in a hospital setting. The RAMQ provides universal coverage for those over the age of 65 years of age and provides coverage during non-employed periods. 42% of the general Quebec population is covered by the RAMQ (24). Moreover, we do not expect that RAMQ coverage would be differential between LMWH groups (25). Third, given the algorithm used to create our study cohort, pregnancy at the

time of VTE was assessed at a time point in the future. This may have introduced immortal time bias given it necessitates survival to the pregnancy event. We expect that this event would be rare given the young median age of our study cohort. Fourth, the incidence of bleeding was calculated based on LMWH dispensed and may not necessarily reflect actual intake (25). However, the use of pharmacy prescription claims to ascertain maternal use of medication in pregnancy has been shown to have a high positive and negative predictive value (26). Fifth, drugs dispensed during hospitalisation are not included in the RAMQ database. We were hence not be able to identify precisely when LWMH was resumed following a delivery or abortive outcome, and timing of resumption has been shown to influence the incidence of postpartum bleeding (27). In women treated with therapeutic anticoagulation, earlier resumption of anticoagulation in the postpartum period has been associated with major hemorrhagic complications, defined as a composite outcome of bleeding requiring surgery, hospital readmission, admission to the intensive care unit, red blood cell transfusion, or fluid resuscitation of 1 liter of more of crystalloids prescribed for bleeding concern (22). Specifically, major hemorrhagic complications were associated with resumption of therapeutic anticoagulation within 9.25 hours of a vaginal delivery, and 15.1 hours of a cesarian delivery (22). To allow us to have a more comprehensive assessment of bleeding, we included antepartum bleeding events in our study, which allowed to evaluate the incidence of bleeding throughout pregnancy. Sixth, misclassification of bleeding outcomes is possible because of coding errors leading to underdiagnosis of bleeding conditions has been reported and may affect our results (28). However, we expect that misclassification would be non-differential between groups. Finally, the assessment of once daily vs. twice daily LMWH dosing required assumptions based on the total quantity of LMWH dispensed in our database. The healthcare databases used allow to identify

the total dispensed dose of a medication prescribed over a specific time period. It does not allow to precisely identify how drugs are prescribed with regards to dosing (once daily, twice daily, thrice daily, etc.). For this reason, we opted to use a 15-day period after cohort entry and assign total dispensed dose > 15 doses as twice daily, and total dispensed dose ≤ 15 doses as once daily. This may have led to exposure misclassification, especially at time of delivery. This finding should be considered as hypothesis generating and requires further study.

Conclusion

This study provides a population-derived estimate of bleeding in pregnant women treated with therapeutic anticoagulation for VTE during pregnancy. Our results show that, while dalteparin is the most used LMWH for this indication in pregnancy, this does not appear to translate into a favourable safety profile compared to enoxaparin or tinzaparin with regards to bleeding complications. Twice daily administration of LMWH may not decrease the risk of postpartum bleeding. Prospective studies evaluating peripartum management of anticoagulation are required to optimize the care of this patient population.

Appendix A. Diagnostic and procedure codes for obstetric-related and non-obstetric related bleeding events

Description	ICD-9	ICD-10	ACTE	CCI	CCADTC
Obstetric-related bleeding events					
Abnormal uterine and vaginal bleeding	626	N93			
Abortion complicated by hemorrhage	6381	O07.1, O07.6			
Antepartum hemorrhage	640	O20, O46, O47			
Peripartum hemorrhage	641.3, 641.8, 641.9	O67			
Postpartum hemorrhage	666	O72			
Postpartum hemorrhage with embolization/ligation/suture of uterus				1.RM.13*, 1.KT.51*, 5.PC.91.LA*	
Hysterotomy			06148, 06265, 06216, 06266, 06270, 06276, 06274, 06273, 06913, 06099	5.CA.89, 1.RM.87, 1.RM.91, 1.RM.89, 1.RS.80, 5.MD.60.RC, 5.MD.60.RD, 5.MD.60.KE, 5.MD.60.CB	80.19, 80.2, 80.3, 80.4, 80.5, 80.6, 86.42
Non-obstetric related bleeding events					
Gastrointestinal site					
Gastroduodenal site	531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6,	K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6,			

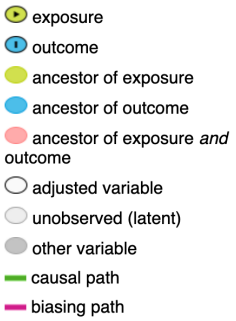
	534.0, 534.2, 534.4, 534.6, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83	K28.0, K28.2, K28.4, K28.6, K29.0, K29.21, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811			
Esophageal site	456.0, 456.20, 530.7, 530.82	I85.01, I85.11, K22.6, K22.8			
Upper gastrointestinal, unspecified	578.0	K92.0			
Lower gastrointestinal site	455.2, 455.5, 455.8, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85	K62.5, K64.4, K64.8, K57.11, K57.13, K57.31, K57.33, K66.1, K62.5, K55.21			
Unspecified site	578.1, 578.9	K92.1, K92.2			
Genitourinary site	593.81, 599.7, 623.8	N28.0, R31.9, R31.0, R31.1, R31.2, N89.8			
Cerebral site	430, 431, 432.0, 432.1, 432.9	I60.9, I61.9, I62.1, I62.0, I62.9			
Other site	423.0, 459.0, 568.81, 719.1, 784.7, 784.8, 786.3	I31.2, R58, K66.1, M25.0, R04.0, R04.1, R04.2,			

		R04.9, R04.8			

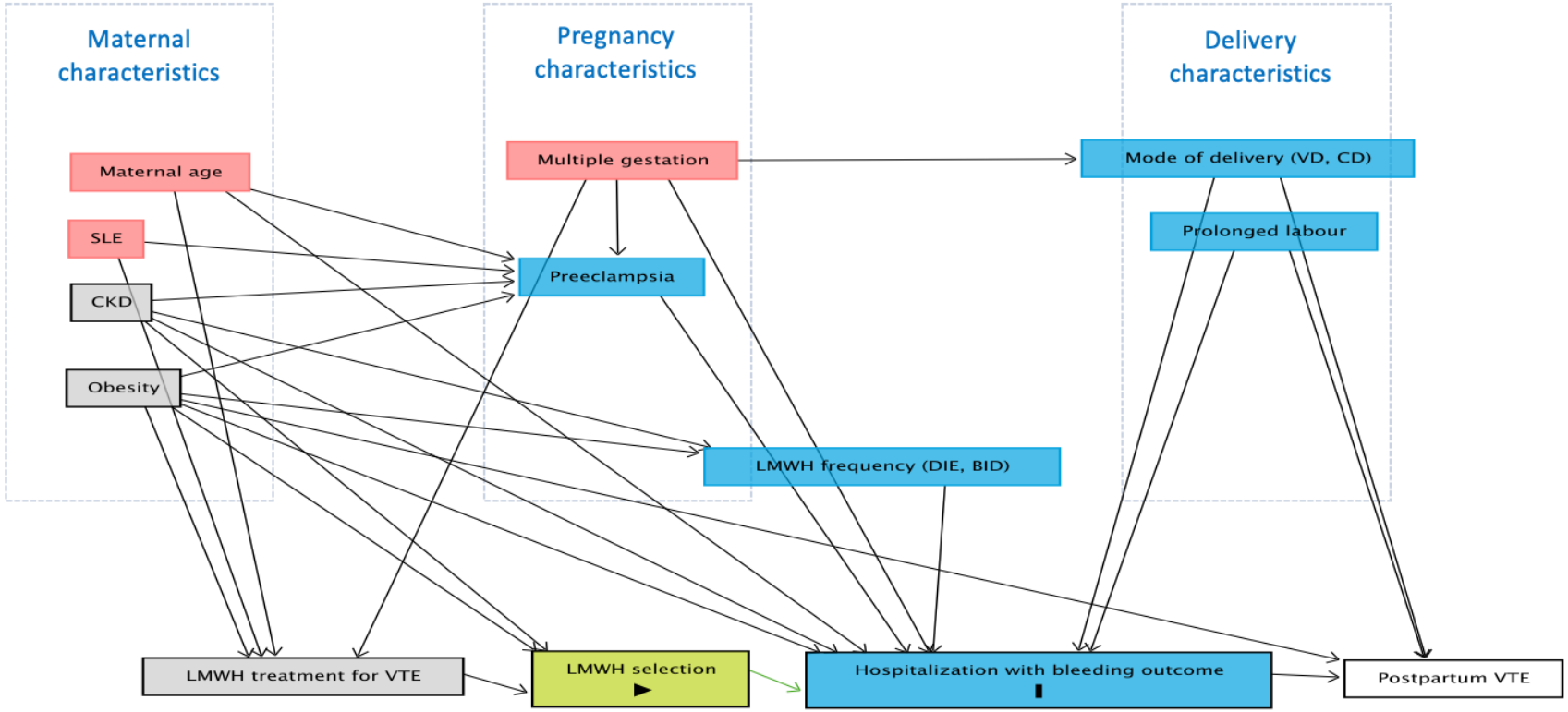
**Include only if ICD code for postpartum hemorrhage*
Abbreviations: CCADTC = Classification canadienne des actes diagnostiques, thérapeutiques et chirurgicaux, CCI = Classification canadienne des interventions en santé, ICD-9 = International Classification of Diseases, 9th Revision, ICD-10 = International Classification of Diseases, 10th Revision.

Appendix B. Adjusted and simplified directed acyclic graphs of the relationship between LMWH selection for VTE in pregnancy and bleeding events

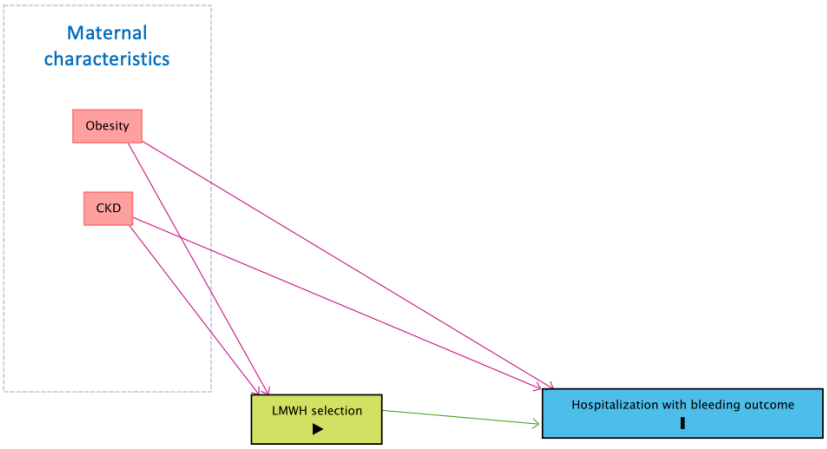
a) Directed acyclic graph colour legend



b) Adjusted directed acyclic graph



c) Simplified directed acyclic graph



Abbreviations: BID = twice daily, CKD = chronic kidney disease, CS =cesarian section, DIE = once daily, LMWH = low-molecular-weight heparin, SLE = systemic lupus erythematosus, VD = vaginal delivery, VTE = venous thromboembolism.

Appendix C. Diagnostic codes for maternal comorbidities and pregnancy characteristics

Description	ICD-9	ICD-10
Maternal characteristics		
Chronic hypertension	401.x-405.x, 642.0x-642.2x, 642.7x	I10-I15, O10.0, O10.9
Gestational hypertension	642.3 *without preeclampsia, eclampsia, or chronic hypertension code	O13x, O16x
Preeclampsia	642.4, 642.5, 642.7	O14.x
Eclampsia	642.6	O15.x
Chronic kidney disease	581.x-583.x, 585.x, 587.x, 588.x, 646.2	N02-N05, N08, N18
Heart disease (any)	412.x-414.x 394.x-397.x, 424.x 428.2, 428.3, 428.4 745.0-747.x, 648.5	I20.x, I25.x I05.x-I08.x I50.2-I50.4 Q20.x, Q22.x, Q25.x-Q27.x, O99.4
Diabetes mellitus	250.x1, 250.x3, 250.x0, 250.x2, 648.8	E10, E11, O24.4, 648.8, O99.8
Hypothyroidism	243.x, 244.x, 245.x	E009, E02, E03, E06, E89
Systemic lupus erythematosus	710.0	M32.1
Anemia	280.1–281.9, 285.9	D50.8, D50.9, D51.x–D53.x
Tobacco smoking	305.1, 649.0	F17.2
Drug use disorder	292.0, 292.8, 292.9, 304.x, 305.2–305.9, 648.3	F11.x–F16.x, F18.x, F19.x, Z71.5, Z72.2
Chronic pulmonary disease	490–492.8, 493.0–493.9, 494.x–505.x, 506.4	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
Malignancy (any)	140.x–172.x, 174.x.–195.8, 200.x–208.x	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x
Obesity	278.0, 649.1, V85.3, V85.4	E66.x

Appendix D. Sensitivity analysis of the risk of major bleeding associated with the use of once vs. twice daily LMWH restricting to VTE occurring as of 30 weeks' gestation

	Patients (n)	Events (n)	Person-years	Incidence rate (95% CI) **	Crude HR (95% CI)
Once daily LMWH	28	*	*	711.5 (18.0-3964.2)	1.0 (Ref)
Twice daily LMWH	9	0	0.7	0	NA

**Any cells with less than 5 patients were suppressed as per RAMQ privacy policy.*
***Per 1000 person-years*
Abbreviations: CI = confidence interval, HR = hazard ratio, n = number of patients, NA = not available, n = number of patients, Ref = reference.

Appendix E. Sensitivity analyses of the risk of major bleeding associated with the use of dalteparin vs. tinzaparin or enoxaparin in patients treated with LMWH for VTE during pregnancy

Analysis	Patients (n)	Events (n)	PY	Incidence rate (95% CI) *	Crude HR (95% CI)
15-day grace period					
Dalteparin	188	12	43.0	279.1	0.7 (0.3-2.1)
Enoxaparin or tinzaparin	71	5	12.4	403.2	1 (ref)
Death assumed on the 1st of the month					
Dalteparin	188	15	49.9	300.4	0.9 (0.3-2.5)
Enoxaparin or tinzaparin	71	5	14.5	345.1	1 (ref)
ITT					
Dalteparin	189	17	306.0	55.6	1.1 (0.4-3.0)
Enoxaparin or tinzaparin	71	5	71.4	70.0	1 (ref)

**Per 1000 person-years*

Abbreviations: CI = confidence interval, HR = hazard ratio, ITT = intention-to-treat, n = number of patients, NA = not available, PY = person-years, Ref = reference.

References

1. Abe K, Kuklina EV, Hooper WC, Callaghan WM. Venous thromboembolism as a cause of severe maternal morbidity and mortality in the United States. Semin Perinatol. 2019;43(4):200-4.
2. James AH. Venous thromboembolism in pregnancy. Arterioscler Thromb Vasc Biol. 2009;29(3):326-31.
3. Chan WS, Rey E, Kent NE, Chan WS, Kent NE, Rey E, et al. Venous thromboembolism and antithrombotic therapy in pregnancy. J Obstet Gynaecol Can. 2014;36(6):527-53.
4. Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018;2(22):3317-59.
5. White RH, Ginsberg JS. Low-molecular-weight heparins: are they all the same? Br J Haematol. 2003;121(1):12-20.
6. Ontario Drug Policy Research Network (ODPRN). Drug Class Review: Low-Molecular-Weight Heparins and Fondaparinux - Final Consolidation Report, 2016. [Available from: https://odprn.ca/wp-content/uploads/2016/05/LMWH-final-consolidated-report-_-May-5-2016.pdf. [
7. Slavik RS, Chan E, Gorman SK, de Lemos J, Chittock D, Simons RK, et al. Dalteparin versus enoxaparin for venous thromboembolism prophylaxis in acute spinal cord injury and major orthopedic trauma patients: 'DETECT' trial. J Trauma. 2007;62(5):1075-81; discussion 81.
8. Michalis LK, Katsouras CS, Papamichael N, Adamides K, Naka KK, Goudevenos J, et al. Enoxaparin versus tinzaparin in non-ST-segment elevation acute coronary syndromes: the EVET trial. Am Heart J. 2003;146(2):304-10.
9. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006;354(14):1464-76.
10. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):92-128.
11. Simard C, Malhamé I, Skeith L, Carson MP, Rey E, Tagalakis V. Management of anticoagulation in pregnant women with venous thromboembolism: An international survey of clinical practice. Thromb Res. 2022;210:20-5.
12. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. J Clin Epidemiol. 1995;48(8):999-1009.
13. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. J Clin Epidemiol. 2004;57(2):131-41.
14. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernández-Díaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. Pharmacoepidemiol Drug Saf. 2013;22(1):16-24.
15. Ailes EC, Simeone RM, Dawson AL, Petersen EE, Gilboa SM. Using insurance claims data to identify and estimate critical periods in pregnancy: An application to antidepressants. Birth Defects Res A Clin Mol Teratol. 2016;106(11):927-34.
16. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. Bmj. 2000;320(7251):1708-12.

17. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf. 2011;20(6):560-6.
18. Ukah UV, Platt RW, Potter BJ, Paradis G, Dayan N, He S, et al. Obstetric haemorrhage and risk of cardiovascular disease after three decades: a population-based cohort study. Bjog. 2020;127(12):1489-97.
19. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC medical research methodology. 2008;8:70.
20. Simard C, Gerstein L, Cafaro T, Filion KB, Douros A, Malhamé I, et al. Bleeding in women with venous thromboembolism during pregnancy: A systematic review of the literature. Res Pract Thromb Haemost. 2022;6(6):e12801.
21. SCHULMAN S, KEARON C, SCIENTIFIC tSOCOAOT, THROMBOSIS SCOTISO, HAEMOSTASIS. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of Thrombosis and Haemostasis. 2005;3(4):692-4.
22. Cote-Poirier G, Bettache N, Cote AM, Mahone M, Morin F, Cumyn A, et al. Evaluation of Complications in Postpartum Women Receiving Therapeutic Anticoagulation. Obstetrics and Gynecology. 2020;136(2):394-401.
23. Merli GJ, Groce JB. Pharmacological and clinical differences between low-molecular-weight heparins: implications for prescribing practice and therapeutic interchange. P T. 2010;35(2):95-105.
24. Devlin RA, Wang Y. Prescription drug expenditures and 'universal' coverage the Quebec experience in Canada. Ottawa: Department of Economics, Faculty of Social Sciences, University of Ottawa; 2016. Available from: http://socialsciences.uottawa.ca/economics/sites/socialsciences.uottawa.ca.economics/files/1609e.pdf.
25. Ramos É, St-André M, Rey É, Oraichi D, Bérard A. Duration of antidepressant use during pregnancy and risk of major congenital malformations. British Journal of Psychiatry. 2008;192(5):344-50.
26. Zhao J-P, Sheehy O, Gorgui J, Bérard A. Can We Rely on Pharmacy Claims Databases to Ascertain Maternal Use of Medications during Pregnancy? Birth Defects Research. 2017;109(6):423-31.
27. Cote-Poirier G, Bettache N, Cote AM, Mahone M, Morin F, Cumyn A, et al. Evaluation of Complications in Postpartum Women Receiving Therapeutic Anticoagulation. Obstetrics & Gynecology. 2020;136(2):394-401.
28. Butwick AJ, Walsh EM, Kuzniewicz M, Li SX, Escobar GJ. Accuracy of international classification of diseases, ninth revision, codes for postpartum hemorrhage among women undergoing cesarean delivery. Transfusion. 2018;58(4):998-1005.
29. Vilain A, Otis S, Forget A, Blais L. Agreement between administrative databases and medical charts for pregnancy-related variables among asthmatic women. Pharmacoepidemiology and drug safety. 2008;17(4):345-53.

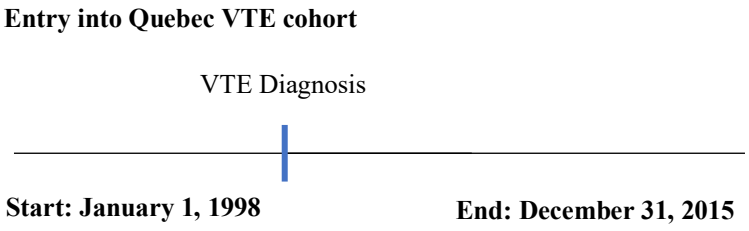
4.3 Supplemental material to cohort study manuscript

4.3.1 Diagnostic codes used to identify venous thromboembolism

Description	ICD-9	ICD-10
Pulmonary embolism	415.x	O882, I269, I260
Deep vein thrombosis	451.x, 453.x, 671.x or 673.x	I801, I828, I829, O223, I822, I820, I802, 0082, I823, O871

4.3.2 Algorithm to build the inception and source populations of pregnant women with venous thromboembolism

1. **Inception cohort**
    a. Identify first VTE diagnostic code within the study period with RAMQ medication insurance coverage at the time of first diagnosis



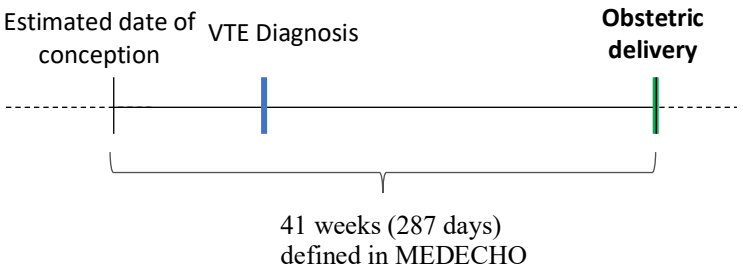
    b. Exclude those less than 18 years of age and above age 55 at the time of first diagnosis
    c. Include individuals continuously insured by the RAMQ for at least 12 months before VTE diagnosis

2. **Source population**
    a. Identify women aged 18-45
    b. Identify the eligibility period

i. If a gestational age (in weeks) is specified in MEDÉCHO, use the gestational age as the eligibility period. For example, if an obstetric delivery code is identified and a 41-week gestational age is present, identify women with VTE diagnosis within that 41-week window (287 days) of the obstetric delivery (29)

c. Identify women aged 18-45 who have an obstetric delivery code (see *4.3.3*), abortive outcome code (see *4.3.4*), hydatidiform mole code (see *4.3.4*), or ectopic pregnancy code (see *4.3.4*), within a specified time period in relation to the index VTE (i.e., eligibility period). The specific time periods vary according to type of code (re: obstetric delivery, abortive outcome, hydatidiform mole, or ectopic pregnancy code).

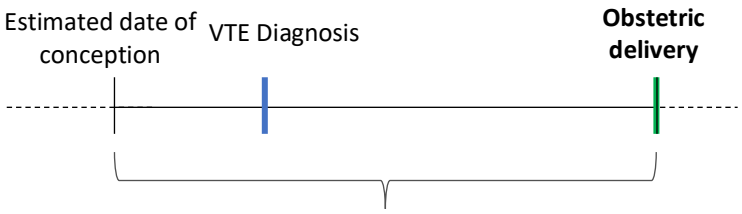
d. There should be at least a calendar day of difference between the index VTE code and the pregnancy outcome code (delivery, abortion or other)



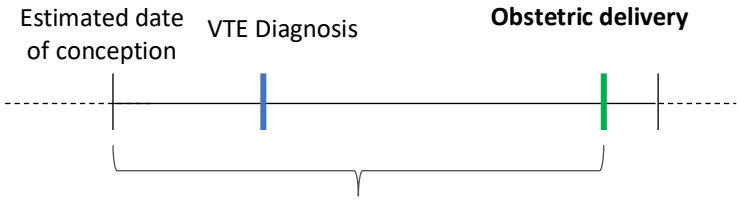
i. If there is no gestational age specified in MEDÉCHO, go to the next step to estimate the gestational age.

e. Gestational age estimation algorithm:

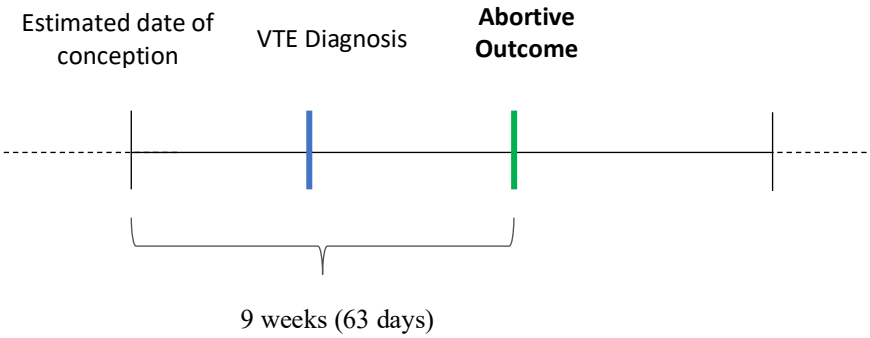
i. If obstetric delivery code (see *4.3.3*) without preterm delivery code, identify women with VTE diagnosis within 39 weeks (273 days) of obstetric delivery (14)



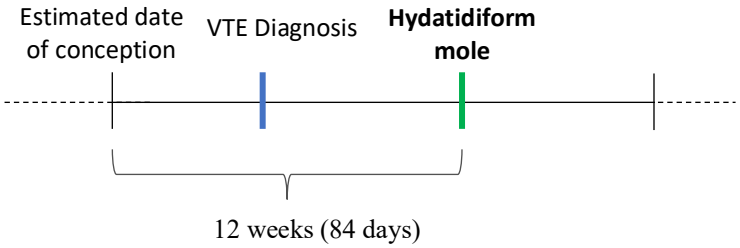
ii. If preterm delivery code (see *4.3.3*), identify women with VTE diagnosis within 35 weeks (245 days) of obstetric delivery code (14)



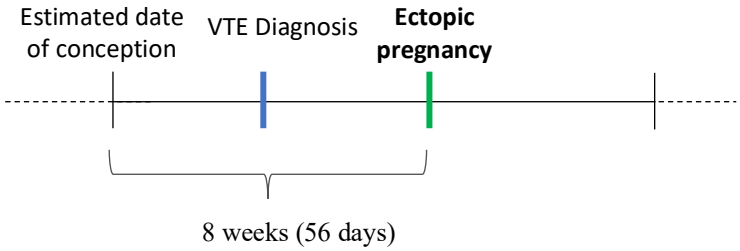
iii. If abortive outcome code ((see *4.3.4*), identify women with VTE diagnosis within 9 weeks (63 days) of abortive outcome (15, 16)



iv. If hydatidiform code (see *4.3.4*), identify women with VTE diagnosis within 12 weeks (84 days) of hydatidiform code (15, 16)



v. If ectopic pregnancy code (see *4.3.4),* identify women with VTE diagnosis within 8 weeks (56 days) of ectopic pregnancy code (15, 16)



4.3.3 Diagnostic codes used to identify obstetric delivery episodes

Description	ICD-9	ICD-10	ACTE	CCI	CCADTC	Eligibility period (if estimated)
Outcome of delivery	V27	Z37				273 days*
Normal delivery	650	O80, O82 (c-section)			87.98	273 days*
Preterm delivery surrogates**	765, 644.0, 644.2	P05, P07, O60.1, P59.0				245 days
Delivery procedures						
Assisted spontaneous delivery					85.69, 84.8, 84.9	273 days*
Vaginal			06903	5.MD.50, 5.MD.51		273 days*
Forceps				5.MD.53	84.61, 84.62, 84.6984.9, 85.3, 84.69, 84.0, 84.1, 84.21, 84.29, 84.3, 84.31, 84.39	273 days*
Breech			06097	5.MD.56	84.51, 84.52, 84.53	273 days*
Vacuum				5.MD.54	84.7, 84.71, 84.79	273 days*
Combination of Forceps and Vacuum				5.MD.55		273 days*
C-section		O82 (c-section)	06912, 06913, 06946	5.MD.60	86.0, 86.1, 86.2, 86.8, 86.9	273 days*
Delivery of second twin			06919			273 days*
SVD after c-section			06950			273 days*
Complex delivery			06945			273 days*

Delivery in water				5.MD.52		273 days*

**273 days unless a preterm delivery code is present. If both delivery and preterm delivery code present, use 245 days.*
Classification canadienne des actes diagnostiques, thérapeutiques et chirurgicaux: CCADTC; Classification canadienne des interventions en santé: CCI; International Classification of Diseases, 9th Revision: ICD-9; International Classification of Diseases, 10th Revision: ICD-10

4.3.4 Diagnostic codes used to identify abortive outcomes

Description	ICD-9	ICD-10	ACTE	CCI	CCADTC	Eligibility period (if estimated)
Hydatiform mole	630	O01			80.0	84 days
Other abnormal product of conception	631	O0281				63 days*
Ectopic	633	O00	06430, 06468,15086, 15095	5.CA.93	86.3	56 days
Abortion	632, 634, 635, 636, 637, 638, 639	O021, O03-O05	06900, 06906, 06908, 06909, 06948, 06949, 06137, 06952, 06451, 16077, 16089, 16093	5.CA.20, 5.CA.24, 5.CA.88, 5.CA.89	87.0	63 days*
D&C following delivery or abortion (incomplete, spontaneous, medical, or missed)				5.PC.91, 5.CA.89	81.01, 87.21, 87.1, 87.29, 81.61	63 days*
Hysterotomy or hysterectomy to terminate pregnancy					86.41, 86.42, 87.71	63 days*

**63 days unless a code for hydatidiform mole or ectopic pregnancy is present, in which case use that eligibility period.*

Classification canadienne des actes diagnostiques, thérapeutiques et chirurgicaux: CCADTC; Classification canadienne des interventions en santé: CCI; International Classification of Diseases, 9th Revision: ICD-9; International Classification of Diseases, 10th Revision: ICD-10

4.3.5 Drug Identification Number (DIN) for low-molecular-weight heparin

LMWH	DIN
Tinzaparin	2167840, 2229515, 2229755, 2231478, 2358158, 2358166, 2358174, 2358182, 2429462, 2429470, 2429489, 2167859, 2056682
Dalteparin	2132621, 2132648, 2132664, 2231171, 2352648, 2352656, 2352664, 2352672, 2352680, 2377454, 2430789, 2132656, 2494582
Enoxaparin	2012472, 2236883, 2378426, 2378434, 2378442, 2242692, 2378450, 2378469, 2236564

CHAPTER 5: DISCUSSION

5.1 Main findings

The overarching objective of my thesis was to answer an unanswered clinical question in the field of VTE in pregnancy: what is the risk of bleeding associated with the use of therapeutic-dose LMWH for the treatment of VTE during pregnancy? We thus performed a systematic review of the literature to evaluate the the existing literature on the topic, followed by a population-basesd cohort study assessing bleeding in this specific patient population.

Our systematic review of the literature reported a wide range of bleeding estimates and highlights the limitations of the existing literature on this topic. We found retrospective cohort studies that used variable bleeding definitions and reported estimates of bleeding complications ranging between 2.9% and 30.0%. Importantly, all studies had important methodological limitations. Most studies did not include a comparator group of patients not receiving anticoagulation, leading to substantial risk of confounding. The subjective assessment of bleeding, which is vulnerable to ascertainment bias, also lead to a significant risk of bias in the measurement of the outcome. Based on the findings of the systematic review of the literature, we highlighted an urgent need for population-derived estimates of bleeding in this patient population to better inform providers and patients.

The objective of the cohort study was to better characterize bleeding complications in women treated for VTE during pregnancy using population-based estimates. To do this, we created a study cohort of women diagnosed with VTE during pregnancy who were treated with LMWH

within 15 days of incident VTE. Given that dalteparin is the most prescribed LMWH in Canada (65), our team wanted to determine if dalteparin was associated with a favourable safety profile with regards to bleeding complications. We hence compared bleeding events associated with dalteparin vs. tinzaparin or enoxaparin and found no significant difference in the incidence of bleeding in both groups. We also found no difference in antepartum or postpartum bleeding between groups. Additionally, physicians often choose to transition to twice daily LMWH dosing for various reasons. Some opt to switch to twice daily dosing at around 20 weeks' gestation given the increase in plasma volume and glomerular filtration rate, which may lead to reduced anti-Xa effects (66). It is unclear whether lower anti-Xa levels lead to a reduced efficacy (66). Other physicians opt to switch to twice daily dosing later in pregnancy, because of a perceived lower bleeding risk around delivery with this dosing (8). Our results suggested that twice daily LMWH dosing, with any LMWH, was not associated with a benefit with regards to bleeding. This may inform practice for healthcare providers who often change to twice daily dosing in the third trimester, a dosing strategy that was common among the respondents of our survey of clinical practice (8).

5.2 Strengths and limitations

We provide the first population-derived estimate of bleeding in this patient population. Our cohort study has several strengths. First, administrative data is collected prospectively, hence independent of the outcome, excluding recall bias (67). Second, it allowed for the identification of traditional bleeding events that are commonly used in the non-pregnant population (68, 69). This includes bleeding that affects the gastrointestinal, genitourinary, and central nervous systems, which are not commonly captured in studies assessing the safety of anticoagulation

during pregnancy (3, 4). Third, while population-derived estimates of bleeding in the general obstetric population are available (70, 71), similar estimates in the anticoagulated pregnant population were not available. This made it difficult for healthcare providers to counsel patients with regards to their risk of bleeding when compared to the general obstetric population. For postpartum bleeding, we now describe an incidence of bleeding that is similar to previously reported incidences in the general obstetric population (70, 71). This should be reassuring to physicians and patients. Fourth, the bleeding estimates provided are representative of multiple healthcare centres, at a provincial level. This minimizes the impact of practice variation of our estimates, especially with regards to peripartum anticoagulation management and timing of postpartum resumption, which may be protocolized differently across variable healthcare institutions, making our findings more generalizable than prior estimates.

Another strength is that we determined postpartum as well as antepartum bleeding. Our systematic review showed that most studies addressing safety and bleeding of anticoagulants during the postpartum period (72). This is also true of studies assessing bleeding in pregnant women treated with various doses of anticoagulation, including prophylactic and intermediate-dose LMWH (42, 48, 73).

We explored the relationship between LMWH dosing and bleeding. This is important given the significant practice variation among healthcare providers with regards to dosing of LMWH around delivery (8). Guidelines recommend once or twice daily therapeutic LMWH during pregnancy given that the benefit of one over the other remains unclear (23, 28). While our findings should be interpreted with caution given the low number of bleeding events and the

assumptions used to identify daily dosing, we provide reassurance that once daily LMWH dosing does not appear to be associated with an increased risk of bleeding. Moreover, it is much easier for patients to inject only once per day, and this dosing strategy may increase compliance (8).

The present thesis has limitations that warrant discussion. Our systematic review of the literature found studies that used heterogeneous bleeding definitions. Given this, it was not meaningful to meta-analyse the bleeding outcomes. While the review was important in highlighting the limitations of the existing literature and provided meaningful descriptions of bleeding events, it was not possible to provide a summary estimate of bleeding in this patient population. However, it provides a critical assessment of the literature and its quality, and identified important knowledge gaps for future research. Furthermore, in the cohort study, we described covariates that may potentially have confounded the relationship between the choice of LMWH and the incidence of bleeding using a directed acyclic graph (Appendix B of cohort study manuscript). We identified chronic kidney disease and obesity as confounders that required adjustment in our model. Unfortunately, the absence of patients with these comorbidities in each LMWH groups prevented us from adjusting our model for these confounders. It is possible that the association between the choice of LMWH and bleeding is not truly confounded by obesity and chronic kidney disease, but future studies are required to evaluate this question further. Moreover, residual confounders in the relationship between the choice of LMWH and the risk of bleeding may have been missed given the observational nature of the study.

The healthcare databases used allow us to identify the total dispensed dose (TDD) of a medication prescribed over a specific time period. It does not allow to precisely identify how

drugs are prescribed with regards to dosing (once daily, twice daily, thrice daily, etc.). For this reason, we used a 15-day period following cohort entry to evaluate the TDD. If the TDD during that 15-day period was > 15 doses of LMWH, we assumed that the prescription was for twice daily dosing, whereas if the TDD was ≤ 15 doses of LMWH, a once daily prescription was assumed. These assumptions may have led to exposure misclassification, especially at time of delivery. Our survey has shown that many healthcare practitioners opt to change from once daily to twice daily LMWH later in pregnancy, closer to the time of induction of labour (8). An example of this misclassification would be if a pregnant patient is diagnosed with a DVT at 8 weeks' gestation and is prescribed therapeutic-dose enoxaparin on that date, she could be treated with once daily enoxaparin on day 16 to 30 following cohort entry, but switched to twice daily dosing later in pregnancy, for example at 36 weeks' gestation. If this patient were to have a PPH requiring a hysterectomy after induction of labour at 40 weeks' gestation, she would have been classified as receiving once daily LMWH when in fact at the time of the hospitalization for bleeding, she had been treated with twice daily LMWH. Realizing this limitation of our analysis and to better evaluate the impact of LMWH dosing around delivery, we opted to perform a sensitivity analysis restricting to VTE events as of 30 weeks' gestation. While the findings of the sensitivity analysis are in line with the primary analysis, it is worth noting that only 37 patients were included in our cohort that had a VTE after 30 weeks' gestation, and given the very small number of events, this should be interpreted with caution.

Finally, our study cohort included women who are covered by the provincial plan and does not include women who are privately insured. Prescription drug expenditure data has shown that 42% of the general population is covered by the RAMQ (74). Our cohort study also includes

women who have antepartum follow-up and delivery in a hospital setting. This may affect the generalizability of our study findings. However, it is unlikely that women with VTE during pregnancy would not seek medical care, and we do not expect that the impact would be differential between both LMWH groups. Additionally, our population-based design used few exclusion criteria during the creation of the study cohort, which likely maximized the generalizability of the results.

5.3 Implications and future work

The systematic review of the literature has highlighted the importance of standardized bleeding definitions in the evaluation of bleeding in the pregnant population. For example, the definition of PPH focuses on a quantity of blood loss within 24 hours of delivery. Many experts have argued that the focus of a bleeding definition should be on the physiological consequences of bleeding, rather than the amount in milliliters (36, 75). They also highlight that standard definitions should move away from distinguishing the amount of blood loss according to the mode of delivery (i.e., vaginal vs. cesarian delivery), given that this distinction has no impact on maternal health related to blood loss (36). The scientific and standardization committee on the control of anticoagulation of the ISTH has proposed a classification of bleeding events into the known ISTH categories of major bleeding, clinically relevant non-major bleeding, and minor bleeding (36). This classification also includes non-obstetric related bleeding events including bleeding in critical organs and bleeding requiring blood product transfusions (36). They recognize that bleeding in pregnant women receiving anticoagulation, regardless of the dose or the indication, is not well described, and highlight the need for standardized definitions (36). Following the publication of our systematic review of the literature, leaders in the field have

published a commentary stating that our systematic review serves as a crucial call to action for higher quality studies and standardized bleeding definitions in this patient population (76). They also highlight the proposed ISTH classification, which is presented in **Tables 7 and 8**.

Table 7. Proposed classification for antepartum and secondary postpartum (24h to 6 weeks after delivery) period (36)

		Major bleeding	CRNMB	Minor bleeding
Antepartum and secondary postpartum periods				
Vaginal bleeding	Prompting a face-to-face evaluation			
	Leading to a hospitalization			
	Leading to antithrombotic therapy modification			
	Related to early pregnancy loss			
Placenta previa				
Placenta abruption				
Fetal or neonatal death (for example bleeding because of placenta abruption)				
Any sign or symptom of hemorrhage including bleeding found on imaging alone	Prompting a face-to-face evaluation			
	Leading to hospitalization or increased level of care			
	Requiring medical intervention by healthcare professional			
Acute clinically overt bleeding	Leading to death			
	That occurs in a critical organ: intracranial, intraspinal, intraocular, retroperitoneal, pericardial,			

	intra-articular, intramuscular with compartment syndrome			
	Associated with a fall in hemoglobin level of 20 g/L or more			
	Leading to transfusion of two or more units of whole or red cells			

Abbreviations: CRNMB: clinically relevant non-major bleeding. Color legend: red = major bleeding, orange = clinically relevant non-major bleeding, green = minor bleeding.

Table 8. Proposed classification for primary postpartum (first 24h of delivery) period (36)

		Major bleeding	**CRNMB**	**Minor bleeding**
Primary postpartum period				
Blood loss < 1000 mL	Alone (including one prophylactic administration of uterotonics)			
Leading to:	Uterus intervention to top bleeding			
	A first line of treatment with uterotonics and/or tranexamic acid			
	Transfusion of two or more units of whole blood or red cells to maintain hemoglobin level > 70-90 g/L			
Blood loss ≥ 1000 mL	Alone			
Leading to:	A first line of treatment with uterotonics and/or tranexamic acid			
	Uterine intervention to stop bleeding			
	A second line of treatment with uterotonics			
	Transfusion of two or more units of whole blood or red cells to maintain hemoglobin > 70-90 g/L			
	Balloon tamponade			
	Embolization			
	Conservative surgery			
	Hysterectomy			

	Death			

Abbreviations: CRNMB: clinically relevant non-major bleeding. Color legend: red = major bleeding, orange = clinically relevant non-major bleeding, green = minor bleeding.

Healthcare database research is a promising avenue for the study of bleeding in women with VTE during pregnancy given the ethical and organizational challenges of randomized controlled trials or of large prospective observational study in this obstetric population with a low event rate. There is a need for validation studies to map existing ICD codes to standardized bleeding definitions, both in the general and pregnant population. Given the recently put forward standardized bleeding definitions for anticoagulated pregnant women, the next step in this field would be to identify outcomes of interest in a more granular way within our healthcare databases. While we were able to identify procedures to control bleeding (PPH requiring embolization or hysterotomy), it would be valuable to link inpatient prescriptions to existing healthcare databases. With this, we would be able to refine our bleeding estimates by identifying the use of uterotonics or tranexamic acid to control bleeding, as well as blood product transfusions during or following delivery. This would provide patients and healthcare providers with more precise bleeding estimates. It would also allow for the identification of risk factors associated with increase antepartum and postpartum bleeding, and it would help providers mitigate those risks when caring for patients. Moreover, given that the timing of resumption of therapeutic-dose anticoagulation in the postpartum period has been associated with the risk of postpartum bleeding in a multicenter study (37), identifying inpatient prescriptions and their timing would allow for population-level assessment of this hypothesis. Ultimately, this could provide data to inform practice guidelines regarding the optimal anticoagulation management during delivery and timing of resumption of LMWH in the postpartum period.

Some questions remain in the assessment of bleeding in this patient population and warrant further study. While the proposed definition for the ISTH committee provides a broad assessment of bleeding antepartum and postpartum, certain consequences of bleeding are not well represented (36). First, surgical complications of cesarian delivery including wound hematomas are not included. With the overall increase in cesarian deliveries in Canada (77), wound hematomas are known to complicate 2-5% of cesarian deliveries and can lead to significant complications including wound dehiscence, wound infection, and prolonged hospital stay (78).

Second, access to epidural anesthesia in the pregnant population receiving therapeutic-dose anticoagulation is not well described. While the induction of labour is recommended by Canadian and American guidelines for this patient population (23, 28), international experts recommend allowing spontaneous labour, with interruption of anticoagulation at the first signs of labour (2). At a higher-than-prophylactic dose of LMWH, the American Society of Regional Anesthesia and Pain Medicine recommend a 24-hour interruption of anticoagulation prior to epidural anesthesia. What remains unclear is in women treated with therapeutic-dose LMWH who enter labour spontaneously, how many are eligible to epidural anesthesia among those who would be agreeable to an epidural. This question is difficult to study using administrative datasets alone given that decision making is primarily based on patient preference, which cannot be captured in administrative data alone, as well as issues of confounding by indication and contraindication.

Finally, various management strategies with regards to anticoagulation management have been proposed. However, how these various options affect patient satisfaction as well as the delivery experience is not known (79). Recently, a multicentre international prospective cohort study evaluating bleeding in women on prophylactic or therapeutic-dose LMWH for VTE-related indications has been funded by the Canadian Institutes of Health Research (80). This study will use the standardized bleeding definition proposed with the ISTH and evaluate important patient-centered outcomes including bleeding, VTE, patient satisfaction and healthcare utilization. These results will inform providers and patients with regards to the optimal anticoagulant management around delivery (80).

CHAPTER 6: CONCLUSIONS

The first objective of my thesis was to summarize the literature with regards to bleeding complications in patients treated with therapeutic-dose LMWH for the treatment of VTE during pregnancy. Our systematic review of the literature provides wide bleeding estimates in this population, ranging between 2.9% and 30.0%. We highlight the limitations of the existing literature with regards to the heterogeneity of bleeding definitions used, and the important risk of bias in the included studies. Our findings identified important knowledge gaps regarding the cumulative incidence of bleeding in this population and clarified the need for standardized bleeding definition in the study of pregnant women on anticoagulation.

The second objective of my thesis was to obtain population-derived estimates of bleeding complications in women treated for VTE during pregnancy using administrative healthcare databases. In our cohort, 7.7% of patient experienced major bleeding, defined as a hospitalization with bleeding or bleeding-related death, yielding an incidence rate of 310.5 per 1000 person-years. This is a substantial risk when compared to the general population treated for VTE, and further studies are required to evaluate bleeding outcomes with more precision within administrative databases, to mitigate factors associated with bleeding in women receiving anticoagulation.

The third objective of my thesis was to compare the incidence of bleeding between the most commonly used LMWH, dalteparin, vs. enoxaparin of tinzaparin. Although different LMWH molecules have distinct pharmacodynamic and pharmacokinetic properties, we found no

significant difference in major bleeding between both groups in overall, antepartum, and postpartum major bleeding.

Our findings highlight the need for standardized bleeding definitions in the study of bleeding in pregnant women. The use of administrative databases is a promising tool in the study of this population, and we put forward the next step in this field, which is to identify outcomes of interest in a more granular way within our databases to better inform providers and patients and improve the care of this patient population.

REFERENCES

1. James AH. Venous Thromboembolism in Pregnancy. Arteriosclerosis Thrombosis and Vascular Biology. 2009;29(3):326-31.
2. Middeldorp S, Ganzevoort W. HEMATOLOGIC COMPLICATIONS IN PREGNANCY How I treat venous thromboembolism in pregnancy. Blood. 2020;136(19):2133-42.
3. Knol HM, Schultinge L, Veeger NJ, Kluin-Nelemans HC, Erwich JJ, Meijer K. The risk of postpartum hemorrhage in women using high dose of low-molecular-weight heparins during pregnancy. Thrombosis research. 2012;130(3):334-8.
4. Roshani S, Cohn DM, Stehouwer AC, Wolf H, van der Post JA, Buller HR, et al. Incidence of postpartum haemorrhage in women receiving therapeutic doses of low-molecular-weight heparin: results of a retrospective cohort study. BMJ Open. 2011;1(2):e000257.
5. Bailly J, Jacobson BF, Louw S. Safety and efficacy of adjusted-dose enoxaparin in pregnant patients with increased risk for venous thromboembolic disease. Int J Gynaecol Obstet. 2019;145(1):70-5.
6. Blanco-Molina Á, Rota L, Di Micco P, Brenner B, Trujillo-Santos J, Ruiz-Gamietea A, et al. Venous thromboembolism during pregnancy, postpartum or during contraceptive use: Findings from the RIETE Registry. Thrombosis and Haemostasis. 2010;103(2):306-11.
7. Chan N, Merriman E, Hyder S, Woulfe T, Tran H, Chunilal S. How do we manage venous thromboembolism in pregnancy? A retrospective review of the practice of diagnosing and managing pregnancy-related venous thromboembolism at two major hospitals in Australia and New Zealand. Internal Medicine Journal. 2012;42(10):1104-12.
8. Simard C, Malhamé I, Skeith L, Carson MP, Rey E, Tagalakis V. Management of anticoagulation in pregnant women with venous thromboembolism: An international survey of clinical practice. Thromb Res. 2022;210:20-5.
9. White RH, Ginsberg JS. Low-molecular-weight heparins: are they all the same? Br J Haematol. 2003;121(1):12-20.
10. Ontario Drug Policy Research Network (ODPRN). Drug Class Review: Low-Molecular-Weight Heparins and Fondaparinux - Final Consolidation Report, 2016. [Available from: https://odprn.ca/wp-content/uploads/2016/05/LMWH-final-consolidated-report-_-May-5-2016.pdf. [
11. Phillippe HM. Overview of venous thromboembolism. Am J Manag Care. 2017;23(20 Suppl):S376-s82.
12. Turpie AGG, Chin BSP, Lip GYH. Venous thromboembolism: pathophysiology, clinical features, and prevention. BMJ. 2002;325(7369):887.
13. Bailly J, Jacobson BF, Louw S. Safety and efficacy of adjusted-dose enoxaparin in pregnant patients with increased risk for venous thromboembolic disease. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2019;145(1):70-5.
14. James AH. Venous Thromboembolism in Pregnancy. Arteriosclerosis, thrombosis, and vascular biology. 2009;29(3):326-31.
15. James AH. Venous thromboembolism in pregnancy. Arterioscler Thromb Vasc Biol. 2009;29(3):326-31.
16. Heavner MS, Zhang M, Bast CE, Parker L, Eyler RF. Thrombolysis for Massive Pulmonary Embolism in Pregnancy. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2017;37(11):1449-57.

17. NIH Office of AIDS Research. HIV/AIDS Glossary: antepartum. https://clinicalinfo.hiv.gov/en/glossary/postpartum. [
18. ACOG Committee Opinion No. 736: Optimizing Postpartum Care. Obstet Gynecol. 2018;131(5):e140-e50.
19. Abe K, Kuklina EV, Hooper WC, Callaghan WM. Venous thromboembolism as a cause of severe maternal morbidity and mortality in the United States. Semin Perinatol. 2019;43(4):200-4.
20. Middeldorp S. How I treat pregnancy-related venous thromboembolism. Blood. 2011;118(20):5394-400.
21. Bates SM, Middeldorp S, Rodger M, James AH, Greer I. Guidance for the treatment and prevention of obstetric-associated venous thromboembolism. J Thromb Thrombolysis. 2016;41(1):92-128.
22. Kourlaba G, Relakis J, Kontodimas S, Holm MV, Maniadakis N. A systematic review and meta-analysis of the epidemiology and burden of venous thromboembolism among pregnant women. Int J Gynaecol Obstet. 2016;132(1):4-10.
23. Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Advances. 2018;2(22):3317-59.
24. Kim NH, Delcroix M, Jais X, Madani MM, Matsubara H, Mayer E, et al. Chronic thromboembolic pulmonary hypertension. The European respiratory journal. 2019;53(1):1801915.
25. Kahn SR. The post-thrombotic syndrome. Hematology Am Soc Hematol Educ Program. 2016;2016(1):413-8.
26. Meissner MH, Moneta G, Burnand K, Gloviczki P, Lohr JM, Lurie F, et al. The hemodynamics and diagnosis of venous disease. Journal of vascular surgery. 2007;46(6, Supplement):S4-S24.
27. Bates SM, Rajasekhar A, Middeldorp S, McLintock C, Rodger MA, James AH, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Adv. 2018;2(22):3317-59.
28. Chan W-S, Rey E, Kent NE, Chan W-S, Kent NE, Rey E, et al. Venous Thromboembolism and Antithrombotic Therapy in Pregnancy. Journal of Obstetrics and Gynaecology Canada. 2014;36(6):527-53.
29. Pregnancy: Venous Thromboembolism Treatment. : Thrombosis Canada, 2018 [Available from: http://thrombosiscanada.ca/clinicalguides/#. [
30. Royal College of Obstetricians and Gynaecologists. Green-top Guideline No. 37a. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. 2015.
31. Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997;337(10):688-98.
32. Anderson DR OBB, Nagpal S, et al. . Economic Evaluation Comparing Low Molecular Weight Heparin with other Modalities for the Prevention of Deep Vein Thrombosis and Pulmonary Embolism Following Total Hip or Knee Arthroplasty. . Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA). 1998.
33. Lovecchio F. Heparin-induced thrombocytopenia. Clin Toxicol (Phila). 2014;52(6):579-83.
34. Merli GJ, Groce JB. Pharmacological and clinical differences between low-molecular-weight heparins: implications for prescribing practice and therapeutic interchange. P T. 2010;35(2):95-105.

35. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost. 2015;13(11):2119-26.
36. Tardy B, Chalayer E, Kamphuisen PW, Ainle FN, Verhamme P, Varlet MN, et al. Definition of bleeding events in studies evaluating prophylactic antithrombotic therapy in pregnant women: A systematic review and a proposal from the ISTH SSC. Journal of Thrombosis and Haemostasis. 2019;17(11):1979-88.
37. Cote-Poirier G, Bettache N, Cote AM, Mahone M, Morin F, Cumyn A, et al. Evaluation of Complications in Postpartum Women Receiving Therapeutic Anticoagulation. Obstetrics and Gynecology. 2020;136(2):394-401.
38. Knol HM, Schultinge L, Veeger NJGM, Kluin-Nelemans HC, Erwich JJHM, Meijer K. The risk of postpartum hemorrhage in women using high dose of low-molecular-weight heparins during pregnancy. Thrombosis Research. 2012;130(3):334-8.
39. Roshani S, Cohn DM, Stehouwer AC, Wolf H, Van Der Post JAM, Büller HR, et al. Incidence of postpartum haemorrhage in women receiving therapeutic doses of low-molecular-weight heparin: Results of a retrospective cohort study. BMJ Open. 2011;1(2).
40. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood. 2005;106(2):401-7.
41. Sirico A, Saccone G, Maruotti GM, Grandone E, Sarno L, Berghella V, et al. Low molecular weight heparin use during pregnancy and risk of postpartum hemorrhage: a systematic review and meta-analysis. Journal of Maternal-Fetal & Neonatal Medicine. 2019;32(11):1893-900.
42. Arbuthnot C, Browne R, Nicole S, Erb SJ, Farrall L, Borg A. A double centre retrospective study into rates of postpartum haemorrhage in women on low molecular weight heparin. British Journal of Haematology. 2017;176(1):141-3.
43. Bauer KA. Use of anticoagulants during pregnancy and postpartum. UpToDate. [
44. Roeters van Lennep JE, Meijer E, Klumper FJ, Middeldorp JM, Bloemenkamp KW, Middeldorp S. Prophylaxis with low-dose low-molecular-weight heparin during pregnancy and postpartum: is it effective? J Thromb Haemost. 2011;9(3):473-80.
45. Bistervels IM, Buchmüller A, Wiegers HMG, Ní Áinle F, Tardy B, Donnelly J, et al. Intermediate-dose versus low-dose low-molecular-weight heparin in pregnant and post-partum women with a history of venous thromboembolism (Highlow study): an open-label, multicentre, randomised, controlled trial. The Lancet.
46. Royal College of Obstetricians and Gynaecologists. Green-top Guideline No. 37a. Reducing the risk of thrombosis
and embolism during pregnancy and the puerperium. 2015.
47. SCHULMAN S, KEARON C, SCIENTIFIC tSOCOAOT, THROMBOSIS SCOTISO, HAEMOSTASIS. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of Thrombosis and Haemostasis. 2005;3(4):692-4.
48. Kominiarek MA, Angelopoulos SM, Shapiro NL, Studee L, Nutescu EA, Hibbard JU. Low-molecular-weight heparin in pregnancy: peripartum bleeding complications. Journal of Perinatology. 2007;27(6):329-34.

49. Galambosi PJ, Ulander VM, Kaaja RJ. A controlled cohort study on the use and safety of low molecular weight heparin during pregnancy. Journal of Thrombosis and Haemostasis. 2011;9:445.
50. Santoro R, Iannaccaro P, Prejanò S, Muleo G. Efficacy and safety of the long-term administration of low-molecular-weight heparins in pregnancy. Blood Coagul Fibrinolysis. 2009;20(4):240-3.
51. Romualdi E, Dentali F, Rancan E, Squizzato A, Steidl L, Middeldorp S, et al. Anticoagulant therapy for venous thromboembolism during pregnancy: A systematic review and a meta-analysis of the literature. Journal of Thrombosis and Haemostasis. 2013;11(2):270-81.
52. Sanson BJ, Lensing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. Thromb Haemost. 1999;81(5):668-72.
53. Economy KE, Valente AM. Mechanical Heart Valves in Pregnancy. Circulation. 2015;132(2):79-81.
54. van Rein N, Biedermann JS, van der Meer FJM, Cannegieter SC, Wiersma N, Vermaas HW, et al. Major bleeding risks of different low-molecular-weight heparin agents: a cohort study in 12 934 patients treated for acute venous thrombosis. Journal of Thrombosis and Haemostasis. 2017;15(7):1386-91.
55. Sharma SK. LOW MOLECULAR WEIGHT HEPARINS. Med J Armed Forces India. 1998;54(3):285-6.
56. Slavik RS, Chan E, Gorman SK, de Lemos J, Chittock D, Simons RK, et al. Dalteparin versus enoxaparin for venous thromboembolism prophylaxis in acute spinal cord injury and major orthopedic trauma patients: 'DETECT' trial. J Trauma. 2007;62(5):1075-81; discussion 81.
57. Michalis LK, Katsouras CS, Papamichael N, Adamides K, Naka KK, Goudevenos J, et al. Enoxaparin versus tinzaparin in non-ST-segment elevation acute coronary syndromes: the EVET trial. Am Heart J. 2003;146(2):304-10.
58. Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006;354(14):1464-76.
59. Zhao X, Yang XX, Ji SZ, Wang XZ, Wang L, Gu CH, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients undergoing percutaneous coronary intervention treated with the glycoprotein IIb/IIIa inhibitor tirofiban. Mil Med Res. 2016;3:13.
60. Michalis LK, Katsouras CS, Papamichael N, Adamides K, Naka KK, Goudevenos J, et al. Enoxaparin versus tinzaparin in non-ST-segment elevation acute coronary syndromes: the EVET trial. American heart journal. 2003;146(2):304-10.
61. Hoppe-Tichy T. New agents in thromboprophylaxis in patients undergoing orthopaedic surgery. EJHP Practice. 2010;16.
62. Pregnancy: Venous Thromboembolism Treatment. : Thrombosis Canada; 2018 [Available from: https://thrombosiscanada.ca/clinicalguides/#.
63. White RH, Ginsberg JS. Low-Molecular-Weight Heparins: Are they all the Same? British Journal of Haematology. 2003;121(1):12-20.
64. Chan WS, Anand S, Ginsberg JS. Anticoagulation of pregnant women with mechanical heart valves: a systematic review of the literature. Arch Intern Med. 2000;160(2):191-6.
65. Ontario Drug Policy Research Network (ODPRN). Drug Class Review: Low-Molecular-Weight Heparins and Fondaparinux - Final Consolidation Report, 2016. [Available from:

https://odprn.ca/wp-content/uploads/2016/05/LMWH-final-consolidated-report-_-May-5-2016.pdf.
66. Rodger M. Pregnancy and venous thromboembolism: 'TIPPS' for risk stratification. Hematology-American Society of Hematology Education Program. 2014:387-92.
67. Blais L, Kettani FZ, Forget A, Beauchesne MF, Lemière C. Asthma exacerbations during the first trimester of pregnancy and congenital malformations: revisiting the association in a large representative cohort. Thorax. 2015;70(7):647-52.
68. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf. 2011;20(6):560-6.
69. Douros A, Filliter C, Azoulay L, Tagalakis V. Effectiveness and safety of direct oral anticoagulants in patients with cancer associated venous thromboembolism. Thromb Res. 2021;202:128-33.
70. Joseph KS, Rouleau J, Kramer MS, Young DC, Liston RM, Baskett TF. Investigation of an increase in postpartum haemorrhage in Canada. Bjog. 2007;114(6):751-9.
71. Mehrabadi A, Hutcheon JA, Lee L, Liston RM, Joseph KS. Trends in postpartum hemorrhage from 2000 to 2009: a population-based study. BMC Pregnancy Childbirth. 2012;12:108.
72. Simard C, Gerstein L, Cafaro T, Filion KB, Douros A, Malhamé I, et al. Bleeding in women with venous thromboembolism during pregnancy: A systematic review of the literature. Res Pract Thromb Haemost. 2022;6(6):e12801.
73. Roeters van Lennep JE, Meijer E, Klumper FJ, Middeldorp JM, Bloemenkamp KW, Middeldorp S. Prophylaxis with low-dose low-molecular-weight heparin during pregnancy and postpartum: is it effective? J Thromb Haemost. 2011;9(3):473-80.
74. Devlin RA, Wang Y. Prescription drug expenditures and 'universal' coverage the Quebec experience in Canada. Ottawa: Department of Economics, Faculty of Social Sciences, University of Ottawa; 2016. Available from: http://socialsciences.uottawa.ca/economics/sites/socialsciences.uottawa.ca.economics/files/1609e.pdf.
75. Menard MK, Main EK, Currigan SM. Executive summary of the reVITALize initiative: standardizing obstetric data definitions. Obstet Gynecol. 2014;124(1):150-3.
76. Saeed K, Áinle FN. Standardizing definitions for bleeding events in studies including pregnant women: A call to action. Res Pract Thromb Haemost. 2022;6(7):e12822.
77. Gu J, Karmakar-Hore S, Hogan M-E, Azzam HM, Barrett JFR, Brown A, et al. Examining Cesarean Section Rates in Canada Using the Modified Robson Classification. Journal of Obstetrics and Gynaecology Canada. 2020;42(6):757-65.
78. Kawakita T, Landy HJ. Surgical site infections after cesarean delivery: epidemiology, prevention and treatment. Matern Health Neonatol Perinatol. 2017;3:12.
79. Coates R, Cupples G, Scamell A, McCourt C. Women's experiences of induction of labour: Qualitative systematic review and thematic synthesis. Midwifery. 2019;69:17-28.
80. Canadian Institutes of Health Research. Funding Decision Database. A prospective cohort study evaluating peripartum anticoagulation management among pregnant women with VTE and its impact on patient outcomes. [Available from: https://webapps.cihr-irsc.gc.ca/decisions/p/project_details.html?applId=434526&lang=en. [