

Management of anticoagulation in pregnant women with venous thromboembolism: An international survey of clinical practice

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ABSTRACT

Introduction: Venous thromboembolism (VTE) is an important cause of maternal morbidity and mortality. During pregnancy, VTE is treated with low-molecular-weight-heparin (LMWH). Studies assessing the optimal duration and peripartum management of therapeutic anticoagulation are lacking. This survey aimed to assess clinician practices for the management of anticoagulation in pregnant women with acute VTE.

Methods: An electronic survey consisting of clinical scenarios addressing anticoagulation management for VTE in pregnancy was created. The target sample was clinicians likely to be involved in the management of pregnant women with acute VTE. The survey completion rate and proportion of individuals selecting a response were determined.

Results: 96 respondents completed the survey including general internists (56.3%), hematologists (21.9%), and obstetricians (6.3%). In the management of a VTE in first or second trimester, most respondents preferred therapeutic LMWH until 6 weeks postpartum. In the first and second trimester, 48.0% and 37.5% of respondents, respectively, opted to reduce the dose of anticoagulation after 3 or 6 months. 29.2% of physicians opted for bridging with intravenous heparin around delivery when treating a VTE in the third trimester. 73.0% perceived an increased risk of clinically relevant non-major bleeding associated with the use of therapeutic anticoagulation in the peripartum and postpartum periods.

Conclusions: The survey highlights a wide variability of practice in the management of therapeutic anticoagulation in pregnancy. Larger scale studies with relevant clinical outcomes including thrombosis and bleeding risks are needed to inform clinical practice.

1. Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important cause of maternal morbidity and mortality. It is estimated to complicate 1 to 2 of 100 pregnancies [1]. The risk of VTE during pregnancy is increased five

to tenfold compared to non-pregnant women of comparable age [2]. Subcutaneous low-molecular-weight-heparin (LMWH) is the standard anticoagulant therapy for acute VTE during pregnancy [3,4]. After an acute VTE, women receive LMWH for a minimum of 3 months, and generally extended for the duration of pregnancy and for at least 6 weeks following delivery, given the additional increased VTE risk during the

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postpartum period [3–6]. Current anticoagulation recommendations in pregnancy are based on observational studies and extrapolation from data in the non-pregnant population [2].

The American Society of Hematology and Thrombosis Canada recommend a scheduled delivery with prior discontinuation of anticoagulation therapy for pregnancy-associated VTE [3,5]. The American College of Obstetricians and Gynecologists recommends either conversion from LMWH to unfractionated heparin (UFH) or interruption of therapeutic LMWH for 24 h prior to a scheduled delivery [8]. These recommendations are based on very low certainty of evidence given the lack of studies assessing the peripartum management of anticoagulation [9]. Moreover, studies on duration of anticoagulation therapy for VTE in pregnancy are lacking. Some societies describe a possible dose reduction after the acute period [4,10] while others recommend therapeutic dose anticoagulation until 6 weeks postpartum [6,11].

Given the variability in recommendations, this survey was created to assess clinician practices, determine variation in practice patterns, and assess the perception of bleeding risk associated with the use of therapeutic anticoagulation for acute VTE during pregnancy. By better understanding practice variation and perception of bleeding risk by clinicians, we can identify priority areas of further research to inform clinical practice.

2. Methods

2.1. Study design and survey development

This was a cross-sectional study using an online survey. The target study population was clinicians experienced in the management of pregnancy-associated VTE. The electronic survey was developed and sent to clinicians including hematologists, general internists, thrombosis, and obstetric medicine physicians internationally. The survey consisted of six multiple choice questions: the first question related to the respondent's clinical specialty, four were two clinical vignettes with two questions each simulating patient encounters discussing the management of VTE in different trimesters, asking about preference regarding anticoagulation dosage and duration, and anticoagulant management preferences at the time of delivery. The last question queried the perceived risk of bleeding associated with therapeutic anticoagulation use during pregnancy according to the International Society on Thrombosis and Hemostasis (ISTH) bleeding definitions of major and clinically relevant non-major bleeding (CRNMB) [12]. ISTH major bleeding is defined as having a symptomatic presentation and 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 more or leading to transfusion of two or more units of whole blood or red cells. CRNMB corresponds to bleeding that does not fit major bleeding criteria, but requires hospitalization, medical intervention, or face-to-face evaluation [12]. A “Other” category was provided for all questions with the option of providing free text answers. Survey questions were pilot tested for relevance and clarity, and the content was validated by four experts in the field of thrombosis and obstetric medicine. The survey was translated from English to French, then back translated to English by two bilingual authors. The full survey can be found in the Supplementary Appendix.

2.2. Study participants

We invited clinicians likely to be involved in the management of pregnant women with acute VTE to participate in the survey. Participants included members of organizations including the Canadian Venous Thromboembolism and Outcomes Research Network (CanVECTOR), the Canadian Society of Internal Medicine (CSIM), the International Society of Obstetric Medicine (ISOM), the North American Society of Obstetric Medicine (NASOM), the Quebec Obstetric Medicine Study Group (Groupe d'étude en médecine obstétricale du Québec,

GÉMOQ) and Thrombosis Canada. In Canada, obstetric medicine experts are general internists or other internal medicine subspecialists who pursue additional training in obstetric medicine, focusing on medical complications in pregnancy, including thrombotic complications. Moreover, in community centers, it is common for a general internist specialist to manage thrombotic complications in pregnancy.

2.3. Survey administration

The survey was administered via *LimeSurvey* [13], an online survey tool hosted on the McGill University server, and was active between September 15 and December 15, 2020. It was distributed in a staggered approach with each society consecutively disseminating the survey via their online newsletter. The survey was also disseminated on Twitter on October 28, 2020, as a strategy to maximize response rates.

2.4. Statistical analysis

Completion rate was measured by calculating the number of participants who completed the survey out of those who agreed to participate. Among participants who completed the survey, the proportion of individuals selecting a response was determined for each question. We performed an exploratory analysis by stratifying responses according to physician speciality and compared responses from respondents specializing in complex pregnancies (i.e., obstetric medicine and maternal fetal medicine) vs. all other respondents using the chi-square or the Fisher exact test. All statistical analyses were performed using R Studio statistical software (version 1.3.1093). Significant associations were defined if *p* values were less than 0.05.

2.5. Ethical considerations

The study was approved by the Research Ethics Board of the Jewish General Hospital in Montreal, Quebec (IRB # 2021-2314).

3. Results

Between September 15 and December 15, 2020, 101 participants responded to the survey, and 96 (95.0%) completed the survey. There were 5 incomplete surveys (5.0%), which were excluded from the analysis. Of the 5 incomplete surveys, all had answered the first question regarding clinical specialty, but none of the clinical scenario questions.

Survey respondents were general internists (54/96, 56.3%), hematologists (21/96, 21.9%), obstetricians (6/96, 6.3%) and other specialists (15/96, 15.6%). 20 respondents (20.8%) were thrombosis experts, 15 (15.6%) were obstetric medicine experts, and four (4.2%) were maternal fetal medicine specialists.

3.1. Acute management and dosing of anticoagulation

The first clinical vignette described a hemodynamically stable patient with a segmental pulmonary embolism with a normal oxygen saturation on ambient air (Supplementary Appendix, Question #2). The event occurred in the first trimester, at 11 weeks' gestation, in the first question and in the second trimester, at 24 weeks' gestation, in the second question (Fig. 1). Regardless of the trimester, most respondents opted to treat the patient with weight-based therapeutic anticoagulation with LMWH during pregnancy until 6 weeks postpartum. For a VTE diagnosed in the first trimester, 48.0% opted to reduce the anticoagulation to intermediate or prophylactic dose after the acute period of 3 to 6 months (Fig. 1). For a VTE diagnosed in the second trimester, 37.5% of respondents opted to reduce the dose to intermediate or prophylactic dose anticoagulation after 3 months of therapeutic dose anticoagulation (Fig. 1). Six of eight (75.0%) of the respondents who opted for the “Other” anticoagulation strategy used weight-adjusted LMWH until delivery then decreased to prophylactic dose anticoagulation until

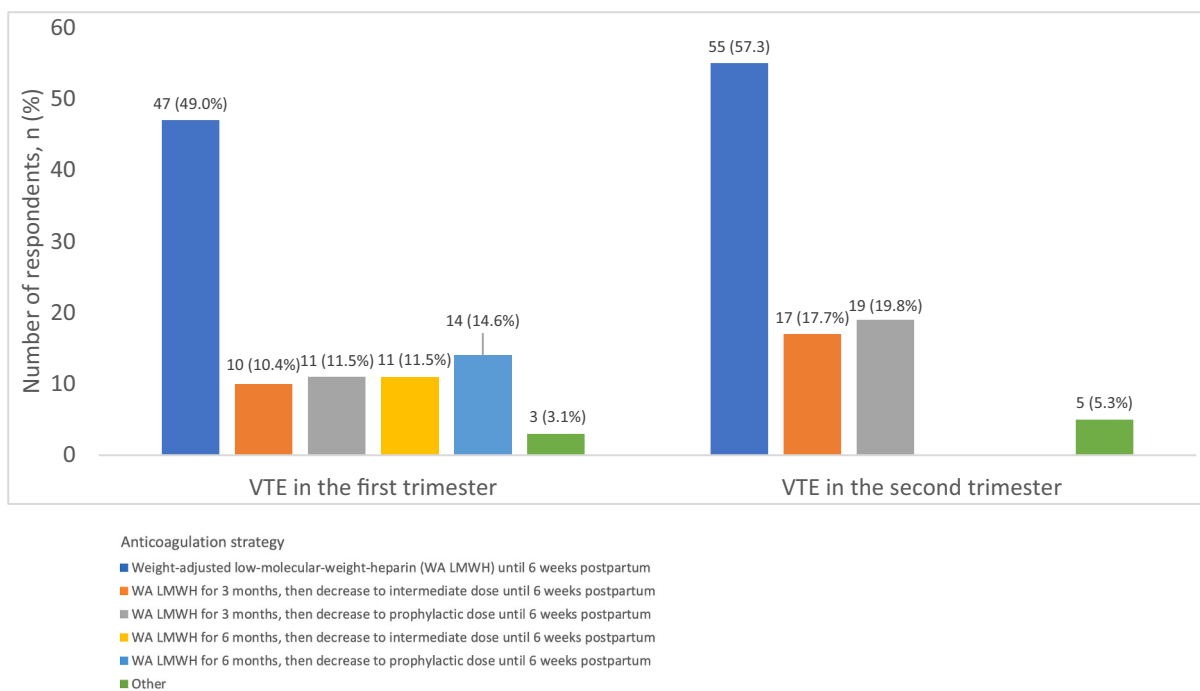


Fig. 1. Management of anticoagulation for a venous thromboembolism in the first vs. second trimester.

6 weeks postpartum. The remaining two respondents opted for hybrid strategies with dose reduction to prophylactic dose anticoagulation after the acute phase until delivery, followed by intermediate dose

anticoagulation for 6 weeks postpartum. There was no difference in the anticoagulation strategy between the two physician specialty groups (χ^2 2.16, *p*-value 0.82 for first trimester VTE, χ^2 1.40, *p*-value 0.71 for

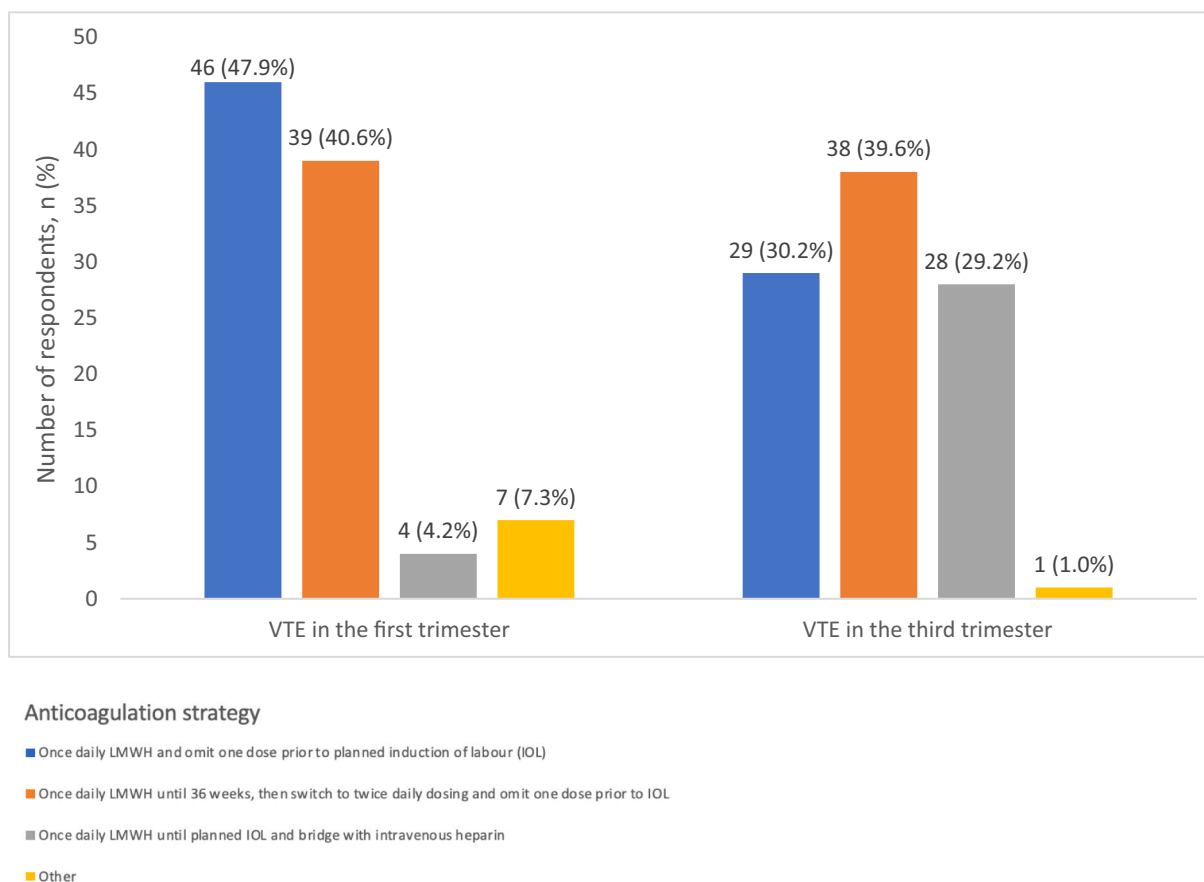


Fig. 2. Peripartum anticoagulation management of a venous thromboembolism in the first vs. third trimester.

second trimester VTE).

3.2. Peripartum anticoagulation management

The second vignette explored the management of therapeutic anticoagulation at the time of delivery (Supplementary Appendix, Question #3). The case described a patient with proximal DVT who was otherwise clinically stable. In the first question, the DVT occurred in the first trimester, at 13 weeks' gestation, and the second question the DVT occurred in the third trimester, at 32 weeks' gestation (Fig. 2). In the management of a DVT at 13 weeks' gestation, 46 respondents (47.9%) opted to treat with once daily LMWH and omit one dose on the day prior to a planned induction of labour, while 39 (40.6%) opted to transition to twice daily dosing at 36 weeks' gestation and omit the dose in the evening prior to the planned induction of labour. Four respondents (4.1%) opted to bridge with intravenous heparin (Fig. 2). Seven respondents (7.3%) opted for other anticoagulation strategies: 5 (5.2%) transitioned to subcutaneous unfractionated heparin at 36 weeks' gestation and opted to either hold at the onset of spontaneous labour or hold the dose prior to induction of labour. The two remaining respondents (2.1%) reduced to prophylactic dose anticoagulation after 3 months and allowed for spontaneous labour. When managing the anticoagulation of a DVT at 32 weeks' gestation, 29 respondents (30.2%) opted to use once daily LMWH and omit one dose the day prior to the induction of labour, 38 (39.6%) transitioned to twice daily dosing at 36 weeks' gestation, and 28 respondents (29.2%) opted to bridge with intravenous heparin (Fig. 2). One respondent (1.0%) opted to transition to twice daily dosing at 36 weeks' gestation and bridge with intravenous heparin the night before induction of labour. There was no difference in anticoagulation strategy according to specialty group (χ^2 2.30, $p = 0.51$ in the first trimester, χ^2 4.85, $p = 0.18$ in the third trimester).

3.3. Respondent perception of bleeding risk

Respondents were asked to comment on their perceived risk of CRNMB associated with the use of therapeutic anticoagulation use

during pregnancy [12] (Fig. 3). 60.0% of respondents perceived an increased risk of antepartum CRNMB and 73.0% perceived an increased risk of CRNMB peripartum and immediately postpartum. There was no difference in perceived bleeding risk according to specialty group (χ^2 0.01, $p = 0.92$).

4. Discussion

In this international survey of varied healthcare professionals regarding the anticoagulation management of VTE during pregnancy and at the time of delivery, we observed substantial practice variations in dosing strategies and peripartum management of anticoagulation. A recently published, smaller North American survey of physician practice patterns in the management of anticoagulation in pregnancy completed by 51 physicians has shown similar variability in the management of VTE, especially with regards to peripartum anticoagulation management [14].

Whether an acute VTE was diagnosed in the first or second trimester, most respondents continued therapeutic dose anticoagulation throughout pregnancy until 6 weeks postpartum. For a VTE in the second trimester, 37.5% reduced the doses after the acute period of 3 months of anticoagulation, to either intermediate or prophylactic dose anticoagulation. Following the acute treatment period of 3 to 6 months, dose reduction of prolonged LMWH has been shown to be safe in the nonpregnant population, such as cancer patients [15,16]. In non-pregnant cancer patients, a LMWH dose reduction after 4 weeks of therapy was shown to be more effective than Warfarin [15]. Patients with cancer are known to have a higher risk of recurrence than pregnant women, which provides rationale for the use of this treatment strategy [17]. While some respondents opted for dose reduction to prophylactic dose anticoagulation, facilitating access to neuraxial anesthesia in the peripartum period, others have opted for intermediate dose anticoagulation. Dose reduction to a higher than prophylactic dose may be justified given the ongoing hypercoagulability of pregnancy [17]. Reducing the dose of anticoagulation may also decrease the need for planned induction of labour, which is known to be associated with an

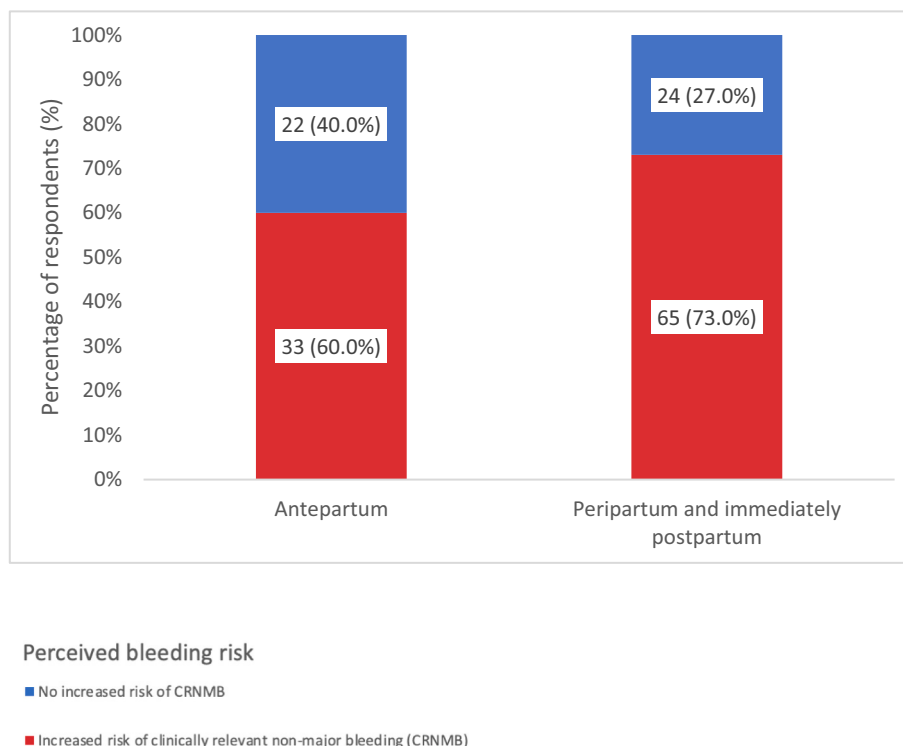


Fig. 3. Physician perception of bleeding risk.

increased risk of postpartum thrombotic events compared to spontaneous onset of labour, likely due to the prolonged duration of anticoagulation interruption [18]. The optimal timing of dose reduction during pregnancy has not been studied and recommendations vary across guidance statements, with some societies describing a possible dose reduction after the acute period [4,19] and others recommending therapeutic anticoagulation until 6 weeks postpartum [6] (Table 1).

As reflected by the different regimens used by survey respondents, both once daily and twice daily LMWH regimens may be used for the treatment of VTE during pregnancy. It is unknown whether these regimens differ with regards to efficacy and safety [22]. Once daily regimens are more convenient and are thought to enhance compliance, and observational studies in pregnancy have not shown an increased risk of recurrence when compared to twice daily schedules [23,24] (Table 1). A significant proportion of respondents opted to transition to twice daily regimens at 36 weeks' gestation and omit the dose the evening prior to induction. This is likely because of the perceived lower risk of bleeding and to improve access to neuraxial anesthesia [25]. In many settings however, a higher than prophylactic dose of anticoagulation requires 24 h of interruption, and twice daily regimens may not improve access to neuraxial anesthesia [26].

We asked respondents about the risk of bleeding associated with therapeutic anticoagulation for VTE during pregnancy. Most respondents perceived an increased risk of CRNMB [12], especially during delivery and the immediate postpartum period. Contradictory evidence exists with regards to the risk of postpartum bleeding associated with therapeutic anticoagulation use [27–29]. A systematic review of 18 studies of 981 pregnant patients with acute VTE reported a weight mean incidence of major bleeding of 1.41% (95% confidence interval (CI) 0.60–2.41%) antenatally and 1.90% (95% CI 0.80–3.60%) during the first 24 h after delivery [30]. A more recent study showed bleeding complications including major, minor hemorrhagic and wound complications of 15.7% (95% CI 8.6–25.3%) [31], which is higher than the prevalence reported in the general population [32]. While less likely to require intensive medical or surgical intervention, minor bleeding and wound complications are known to affect quality of life in women recovering after vaginal birth or cesarean section [33]. Substantial heterogeneity in the reported ante-, peri-, and postpartum bleeding definitions in individual studies precludes definite conclusions about peripartum bleeding risks [30].

This study has some limitations. First, the responses from scenario-based questions may not represent actual physician behaviours [34,35]. While this was addressed by creating scenarios that closely resembled real patients encountered that were vetted by context experts, the vignettes may be more representative of North American practice, with some international experts allowing for spontaneous labour in women on therapeutic dose anticoagulation [9]. The type and dose of anticoagulation was not specified in the survey and was left to the interpretation of the respondent as an attempt to be as inclusive as possible and to reflect local practices. Second, maternal-fetal medicine experts and general obstetricians were underrepresented because the survey was not sent to obstetrics and gynecology societies. Those who did answer the survey could have been members of NASOM, ISOM, or may have answered the survey via Twitter. The majority of respondents were general internists, including obstetric medicine and thrombosis medicine experts. In Canada, general internists commonly manage VTE in pregnancy. This practice may not be generalizable to other countries. Third, internal consistency measurements and test-retest reliability were not performed. Fourth, because the survey was open and disseminated online, including via Twitter, it was not possible to reliably estimate the number of individuals reached in total, precluding the calculation of a response rate [36]. Lastly, the number of respondents by specialty may have been too small to detect differences in responses by specialty.

Table 1
Society recommendations for treatment of venous thromboembolism in pregnancy.

Society	Anticoagulant dosing	Anticoagulant duration	Peripartum management of anticoagulation
American Society of Hematology [3]	Either once-per-day or twice-per-day dosing regimens are recommended.	NA	Scheduled delivery with prior discontinuation of therapeutic dose anticoagulant therapy.
American College of Chest Physicians [11]	A decrease in dosing intensity later in therapy to 75% of a full-treatment dose may be useful in women at risk of anticoagulant-related bleeding.	Anticoagulants should be used for at least 6 weeks postpartum (for a minimum total duration of therapy of 3 months).	For women receiving adjusted-dose LMWH therapy and where delivery is planned, discontinuation of LMWH at least 24 h prior to induction of labour or cesarean section is recommended.
Society of Obstetricians and Gynecologists of Canada [20]	LMWH can be administered once or twice a day depending on the agent selected. Following initial treatment, anticoagulation intensity can be decreased to intermediate or prophylactic dose for the remainder of the pregnancy and for at least 6 weeks postpartum.	Therapeutic anticoagulation for a minimum of 3 months is recommended.	Discontinue prophylactic or intermediate dose LMWH or UFH upon the onset of spontaneous labour or the day prior to a planned induction of labour or cesarean section.
American College of Obstetricians and Gynecologists [8]	Adjusted-dose anticoagulation is recommended. LMWH should be administered once or twice daily. Although a moderated intensity of anticoagulation after a full-dose treatment for 3–6 months, the safety of this approach in pregnancy is unknown because the provoking factor is unresolved.	Adjusted dose LMWH/UFH for a minimum of 6 weeks postpartum.	Women receiving anticoagulation therapy may be converted from LMWH to UFH in anticipation of delivery. An alternative option may be to stop anticoagulation and induce labour within 24 h.
Thrombosis Canada [5]	LMWH dosing is adjusted according to the actual body weight at time of diagnosis and once daily is preferred than twice daily due to patient convenience.	A minimum total duration of 3 months is recommended. Given the additional increase in risk of VTE during pregnancy and the postpartum period, treatment is generally extended throughout pregnancy and for at least 6 weeks postpartum.	Patients taking once daily therapeutic LMWH should take their last dose >24 h prior to scheduled induction or cesarean section to allow for neuraxial anesthesia and safe delivery.

Abbreviations: LMWH: low-molecular-weight-heparin; NA: not available; UFH: unfractionated heparin; VTE: venous thromboembolism.

5. Conclusion

This international survey of physicians highlights a considerable variation in practice with regards to VTE treatment during pregnancy, as well as and peripartum anticoagulation strategies. Ongoing studies assessing relevant and standardized clinical outcomes such as bleeding, VTE, as well as patient preferences and values relating to labour and delivery planning will provide much needed guidance to physicians managing VTE during pregnancy.

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Author contribution

All authors of this research paper have directly participated in the planning, execution, or analysis of the study as well as the creation of this manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.thromres.2021.12.016>.

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