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Online first version

How I treat pregnancy-related venous thromboembolism

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Abstract

Venous thromboembolism (VTE) complicates approximately 1 to 2 of 1,000 pregnancies, with pulmonary embolism (PE) being a leading cause of maternal mortality and deep vein thrombosis (DVT) an important cause of maternal morbidity, also on the long term. However, a strong evidence base for the management of pregnancy-related VTE is missing. Management is not standardized between physicians, centers and countries. The management of pregnancy-related VTE is based on extrapolation from the non-pregnant population and clinical trial data for the optimal treatment are not available. LMWH in therapeutic doses is the treatment of choice during pregnancy, and anticoagulation (LMWH or vitamin K antagonists postpartum) should be continued until 6 weeks after delivery with a minimum total duration of 3 months. Use of LMWH or vitamin K antagonists does not preclude breastfeeding. Whether dosing should be based on weight or antiXa levels is unknown, and practices differ between centers. Management of delivery, including the type of anesthesia if deemed necessary, requires a multidisciplinary approach, and several options are possible, depending on local preferences and patient-specific conditions.

Introduction

During pregnancy and the postpartum period, women are at increased risk of venous thromboembolism (VTE). Pulmonary embolism (PE) is a leading cause of maternal mortality in the Western world and deep vein thrombosis (DVT) in pregnancy is an important cause of maternal morbidity, also on the long term.¹⁻³ VTE complicates approximately 1 to 2 of 1,000 pregnancies, and the risk increases with age, mode of delivery, and presence of comorbid conditions.^{1;4;5} In the general population, the incidence is 1 to 2 per 1000 person-years, but in young women this risk is considerably lower.⁶ During pregnancy, the risk is increased approximately 5-fold compared to age-matched non-pregnant women, but in the postpartum period the relative risk has been found as high as 60-fold during the first 3 months after delivery.⁷ Approximately two-thirds of deep vein thromboses (DVT) of the leg occur antepartum, with these events distributed more or less equally over all trimesters.⁸ Given the much longer duration of the antepartum period than the postpartum period, the daily absolute risk of VTE is highest postpartum. The epidemiology of PE appears to differ slightly from DVT, with the majority of pregnancy-related episodes of PE occurring in the postpartum period.⁴

Despite these strong risk increases and high absolute risks, a strong evidence base for the management of pregnancy-related VTE is missing. It is striking that, contrary to non-pregnant patients, diagnostic strategies, therapeutic options, and preventive measures for VTE in pregnant and postpartum women have not been addressed adequately in well-sized observational or intervention studies. Therefore, management is not standardized between physicians, centers and countries. In this review, I will discuss how I treat pregnancy-related VTE based on a patient history from my clinical practice in an academic hospital in The

Netherlands.

Case history

A 33 year-old pregnant woman presented to the emergency department with shortness of breath and thoracic pain on the left side that increased with inspiration. She had been hospitalized 10 days earlier in Italy, because of vaginal bleeding in the 15th week of her third pregnancy. Ultrasound had revealed a small retroplacental hematoma with normal vital signs of the fetus. She had been immobilized for 3 days and the bleeding had subsided. She had not received thrombosis prophylaxis. After hospital discharge, she had travelled back to The Netherlands, a 12-hour trip by car. Her previous medical history was uneventful; she had had two uncomplicated pregnancies, and her family history was negative for VTE. At physical examination she appeared short of breath and in pain, with respiration of 24 excursions per minute, temperature 37.2 degrees Celsius, blood pressure 110/70 mmHg, regular pulse 98 beats per minute, transcutanic oxygen saturation 97% at room air, and no abnormalities at chest examination. She had no symptoms or signs of deep vein thrombosis. First, a bilateral compression ultrasound of the legs was performed and showed normal compressibility of the femoral and popliteal veins on both sides. Second, since there was no alternative diagnosis, a spiral CT scan was performed and revealed multiple bilateral pulmonary emboli.

Our patient was treated with twice-daily LMWH (nadroparin 7,600 IU bid) for the first 5 days while she was admitted to the obstetric ward. Her chest pain subsided in a few days, but she remained somewhat short of breath throughout pregnancy. She had no recurrent vaginal bleeding. After hospital discharge, she was treated with LMWH once-daily (nadroparin 15,200 IU), which she tolerated well apart from some mild bruising around the injection sites. She had adequate peak antiX-levels throughout pregnancy, and normal platelet counts. She went into spontaneous labour, at a gestational age of 38 weeks, and delivered a healthy

newborn girl 22 hours after the last injection of LMWH. Blood loss was estimated to be 350 mL, and LMWH was re-started 12 hours after delivery, at half a daily dose (i.e. nadroparin 7,600 IU), and at full-dose 12 hours thereafter, in the once-daily regimen (i.e. nadroparin 15,200 IU). She preferred LMWH continuation over switching to vitamin K antagonists, and stopped her anticoagulant treatment 6 weeks after delivery. Her shortness of breath had disappeared completely shortly after delivery, and she did well on follow-up.

Several clinical decisions that were made in the management of this patient, all taken within the course of a few hours at the emergency department, are worth discussing. I will describe my considerations in the following paragraphs. After the diagnosis of VTE in pregnancy I will describe the evidence regarding efficacy of anticoagulation in pregnancy, fetal and maternal safety issues, management of delivery and the postpartum period.

Diagnosis of VTE in pregnant women

Studies on the diagnostic management strategies of deep vein thrombosis and pulmonary embolism have excluded pregnant women, and only few studies have addressed the utility of empirical clinical probability assessment or a pregnancy-specific clinical decision rule, with or without the use of d-dimers.^{9;10} Given the small patient numbers in these studies with a low prevalence of DVT or PE, and the fact that d-dimers are often increased during pregnancy, objective imaging remains the cornerstone of diagnosis and is crucial to avoid treating women who don't have VTE.¹¹ Imaging techniques of the lungs should take into account the radiation exposure of the fetus. Multi-detector row helical CT scanning carries the lowest fetal radiation exposure of approximately 0.013 mSv, compared to 0.026 for single detector row CT and at least 0.11 mSv for perfusion scintigraphy (depending on the protocol and without taking

ventilation scintigraphy into account.^{12;13} Pulmonary angiography via the brachial route exposes the fetus to less than 0.5 mSv, whereas via the femoral route this is estimated to be between 2.21 and 3.74.¹² All these fetal radiation exposure rates are much lower than the threshold dose for induction of malignancies (100 mSv) and justifies the use of diagnostic testing involving radiation in pregnancy for the exclusion of potentially fatal VTE.

Although the diagnostic yield of compression ultrasonography of the legs is low in asymptomatic women, it is a reasonable approach to avoid radiation in women suspected of PE. Obviously, ultrasound testing should not lead to diagnostic delay, and if negative must prompt objective diagnostic testing of the lungs. Algorithms in pregnant women with suspected PE proposed are shown in the Figure.¹¹

Management of VTE in pregnancy

Anticoagulant drugs of choice in pregnancy – efficacy in pregnancy

Pregnant women have been excluded from all major trials investigating various treatment regimens in acute VTE. In the non-pregnant population, the initial use of LMWH for treatment of acute VTE is firmly established and doses are based on body weight, with similar efficacy of once versus twice daily regimens.^{14;15} Also, long-term treatment with LMWH has shown to be at least, and in cancer patients more effective than VKA to prevent recurrent VTE.^{16;17} Nevertheless, several issues about the use of therapeutic doses of LMWH in pregnant women remain controversial. First, it is unclear whether a pre-pregnancy weight can be used to determine the appropriate dose of LMWH, or whether dose adjustments are required as the pregnancy progresses and body weight increases. Second, since the volume of distribution of LMWH changes and glomerular filtration rate increases in the second trimester, it is unclear whether a twice-daily regimen should be preferred over a once-daily

regimen. Many clinicians use a once daily regimen to simplify administration and enhance compliance, and prospective observational studies have not demonstrated an increase in the risk of recurrence with the once daily regimen over the twice daily regimen.^{18;19} For the initial treatment of acute VTE in pregnancy in hospital, I use a twice-daily regimen based on actual body weight. However, in order to limit the number of injections and subsequent risk of skin reactions, and the absence of convincing evidence that pregnant women do less well on a once-daily compared to twice-daily regimen, I switch to a once-daily regimen after a few days or at hospital discharge.

Data from pharmacokinetic studies of various LMWHs in pregnant women have shown conflicting results with regard to the need for dose-escalation to maintain levels within the therapeutic range.²⁰⁻²⁵ The ACCP guidelines are unable to provide a specific advice about anti-Xa level monitoring, in the absence of large studies using clinical endpoints demonstrating that there is an optimal therapeutic anti-Xa LMWH range or that dose-adjustments increase the safety or efficacy of therapy.²⁶ Despite these uncertainties, I monitor anti-factor Xa levels four hours after injection and target to an anti-Xa level of 0.8 to 1.6 with a once-daily regimen of LMWH (0.6 to 1.0 units/mL if a twice-daily regimen is used) at infrequent intervals, and combine this with the platelet monitoring as described above. An important practical advice is to instruct women to inject themselves in the morning, in order to meet the four-hour post-injection time point of blood withdrawal.

The optimal intensity and duration of anticoagulation is an issue that has been addressed extensively in the non-pregnant population.¹⁵ Based on the CLOT trial in cancer patients with VTE, a dose reduction of LMWH to 75% of full dose after the first month is considered reasonable according to the ACCP guidelines, particularly for women who are at increased risk for bleeding.^{17;26} However, I treat women with acute VTE with full adjusted-dose LMWH throughout their pregnancy, based on the assumption of increased efficacy of the higher dose,

the continuing presence of the risk factor of pregnancy, and the absence of evidence that a 75% of full adjusted-dose reduces the risk of bleeding in pregnant women. Regarding duration, I treat women until 6 weeks postpartum, since the daily risk in any woman to develop VTE is highest during this period.⁷ Extrapolating the optimal duration of anticoagulation of non-pregnant patients with a VTE provoked by a major temporary risk factor, the minimum duration should be 3 months, so this postpartum treatment may be longer if VTE occurred in late pregnancy.¹⁵

Anticoagulant drugs of choice in pregnancy – fetal safety

The drug of choice in the treatment of VTE in pregnant women takes into account the safety for both mother and fetus, and the efficacy of anticoagulant drugs for the pregnant woman herself. With respect to fetal safety in terms of their potential to induce fetal harm (teratogenicity, congenital malformations, fetal bleeding), there is ample experience with unfractionated heparin and low-molecular-weight heparins (LMWH) in pregnant women. These agents do not cross the placenta and are considered safe to use in pregnancy, based on numerous observational studies.^{26;27}

In contrast, vitamin K antagonists cross the placenta and the induced vitamin K deficiency in the fetus may cause coumadin embryopathy, a disorder that is characterized by nasal hypoplasia and stippled epiphyses.²⁸ This teratogenic effect is only present when vitamin K antagonists are taken in the 6th to 12th weeks of gestation (defined as weeks after the first day of the last menstrual cycle). When vitamin K antagonists are used throughout pregnancy, as is sometimes done in women with mechanical heart valves, the risk of congenital abnormalities is estimated between 4 and 10%.^{29;30} Although generally considered safe during the second trimester of pregnancy, careful examination of school-aged children who had been exposed to vitamin K antagonists in utero during the second and/or third trimester revealed a 2-fold

increased risk of minor neurological dysfunction or a lower than 80 intelligence quotient (IQ) (OR 2.1; 95%CI 1.2-3.8).^{31;32} Therefore, I avoid the use of these agents throughout the entire pregnancy for the indication of treatment of prophylaxis of VTE, unless in rare cases where maternal side effects limit the use of LMWH. In the third trimester, the bleeding risks for the fetus, particularly during delivery, are a reason to avoid vitamin K antagonists during this time.

Other heparin-like anticoagulants, such as danaparoid and fondaparinux, have been and are increasingly being used in pregnancy, although the experience in human pregnancies is limited.^{26;33} Furthermore, minor anticoagulant activity could be detected in fetal cord blood in five neonates of mothers who were treated with fondaparinux, indicating some placental transfer of the pentasaccharide.³⁴ Despite the limited placental transfer, I prefer fondaparinux over vitamin K antagonists in pregnant women who have developed allergic skin reactions to several LMWH preparations or have a history of heparin-induced thrombocytopenia, or, alternatively, twice daily administration of danaparoid.

Although thrombolysis is contraindicated in pregnancy, several case reports have been described of its use in pregnant patients with massive PE.^{35;36} Recombinant tissueplasminogen activator and streptokinase are large molecules that do not cross the placenta, whereas urokinase does.³⁵ Bearing in mind publication bias of cases with a positive outcome, a recent literature review of 13 patients observed a risk of fetal death of 15% and of preterm delivery of approximately 30%.³⁵ In my opinion, thrombolysis should be reserved for hemodynamically instable women with PE and in whom risks to the fetus and risk of severe bleeding in the mother must be accepted in view of her life-threatening condition.

There is no place for new oral anticoagulants, i.e. direct thrombin inhibitors and anti-Xa inhibitors, in pregnancy, and there appears to be animal toxicity according to the manufacturer's summary of product characteristics. A few case reports have described the use

of parenteral thrombin inhibitors in pregnancy, but these data are insufficient to conclude on their safety in pregnant women.²⁶

Anticoagulant drugs of choice in pregnancy – maternal safety

The most obvious maternal safety issue of any anticoagulant is the risk of bleeding, both antepartum as well as around delivery and in the postpartum period. The risk of significant bleeding with the use of LMWH in pregnant women is generally reported to be around 2%, and as being mostly related to obstetric causes.²⁷ However, these data are based on observational studies including numerous case reports, and may be biased by selective publication of successful patient histories and underreporting of complications. Furthermore, in most recent reports of relatively large numbers of women using LMWH during pregnancy, women using therapeutic dose LMWH for acute VTE were underrepresented, and the assessment for this specific patient group suffers from incompleteness of data to deduce the correct denominator.³⁷⁻³⁹ When therapeutic doses are employed, the incidence of major bleeding was estimated to be 1.72% (95% CI, 0.36%-5.00%) in a systematic review of 15 studies (including 6 case reports) reporting 174 women who had been treated for acute VTE.²⁷ In a prospective evaluation of 126 pregnant women with acute VTE in the UK and Ireland, the risks for bleeding during pregnancy was 6%, with none of the episodes considered by the authors as major bleeding, although these included episodes of rectal bleeding from endometriosis and haemoptysis.¹⁸ The risk of postpartum hemorrhage (>500 mL of blood loss) was 5% in the first 24 hours after delivery, and secondary major postpartum hemorrhage occurred in 2% of the women in the days thereafter. In another retrospective study of 55 women of whom 37 were treated with LMWH doses targeted at antiXa levels of 0.5 to 1.0, the risk of postpartum hemorrhage was 5.7%.⁴⁰ We retrospectively identified 83 women who had been treated with therapeutic doses of LMWH in the Academic Medical Center in

Amsterdam, and found the incidence of postpartum hemorrhage to be around 10%, which was not statistically different from a cohort of women who delivered in our hospital and who were not treated with anticoagulants.⁴¹

Besides the potential increased risk for bleeding from obstetric causes, it is important to note that the use of therapeutic dose LMWH precludes the use of neuraxial anesthesia, because of the (very low) risk of neuraxial hemotoma. In these high doses, LMWH should be discontinued at least 24 hours prior to regional anesthesia, and not restarted until 24 hours after catheter removal.⁴² Discontinuation of anticoagulation for 48 hours or longer is not attractive in the setting of treatment of acute VTE (see also the section *Management of delivery*).

Other side effects of LMWH are the nuisance of daily injections. The long-term use of subcutaneously administered LMWH in pregnant women frequently leads to skin reactions, which are mainly type IV delayed hypersensitivity reactions at the injection site of subcutaneously administered LMWH.⁴³⁻⁴⁵ In a retrospective analysis of 66 consecutive women treated with LMWH in two university hospitals in The Netherlands, we switched to another LMWH preparation in 25% of our patients who had developed skin complaints after a median duration of 26 days (range 7 to 95).⁴³ Of these women, about one-third also developed complaints with the use of another LMWH. If no symptoms or signs of type I allergy are present, I pragmatically switch to another LMWH.⁴⁶ If all registered LMWHs lead to skin problems, danaparoid sodium or fondaparinux can be considered, with the limitation of having less safety data (as outlined previously in the paragraph about fetal safety).

Rare maternal complications of heparins are heparin-induced thrombocytopenia (HIT) and osteoporosis. The incidence of HIT in pregnant patients who are only treated with LMWH is considered very low (<0.1%),²⁷ and therefore the grade 2C recommendation in the most recent ACCP guideline is to not routinely monitor platelet counts.⁴⁷ The risk of HIT is

assumed to be somewhat higher (between 0.1 and 1%) if pregnant women have been exposed to unfractionated heparin prior to LMWH treatment, leading to a grade 2C recommendation to monitor platelet counts more frequently from day 4 for at least 14 days.⁴⁷ However, these are weak recommendations and given the potential underreporting bias in patient series on which these risk estimates are based, as well as the fact that platelet monitoring can be easily combined with other routine blood tests during pregnancy (such as hemoglobin levels), I monitor platelets at baseline and between 4 and 12 days post-initiation of therapy, at a time that is most practical for the patient if she is treated outside the hospital; and at infrequent intervals (6 to 8 weeks, coinciding with obstetric follow-up visits) thereafter. Long-term unfractionated heparin use is known to cause symptomatic osteoporosis in up to 2% of patients.⁴⁸ Small studies of bone density in pregnant women receiving prophylactic doses of LMWH suggest that use of this medication does not induce more bone loss as compared to pregnant women who did not receive LMWH.^{49;50} Whether the risk of symptomatic osteoporosis with therapeutic doses of LMWH is increased, is unknown. I do not routinely measure bone density, nor do I take preventive measures in women receiving LMWH during pregnancy.

Intravenous unfractionated heparin to achieve a therapeutic activated partial thrombin plasma time (APTT) is a reasonable short-term option, particularly for women in whom the need for rapid counteraction of the anticoagulant effect is anticipated, for instance because of an increased risk for bleeding or imminent delivery. Unfractionated heparin has a very short half-life and can be completely counteracted by protamine sulfate, although there are no solid safety data of the latter agent in pregnancy. In my personal experience however, these presumed benefits are often counterbalanced by difficulty in achieving APTTs in the desired range, with the obvious risk of extending thrombosis as a result of under-treatment in a woman with acute VTE, and over-anticoagulation in a woman in whom this option is chosen

because of an increased risk of bleeding. In such patients, I personally prefer a twice-daily LMWH regimen based on actual body weight over intravenous unfractionated heparin, with the theoretical rationale that peak antiXa levels are somewhat lower (at a similar area under the curve) than with a once-daily regimen,⁵¹ and that in case of a bleeding emergency, LMWH can still be partially neutralized by protamine sulfate.

Although unfractionated heparin can be administered subcutaneously and dose adjustments can be made based on APTTs, the short half-life leads to the need for a twice-daily dosing regimen. Furthermore, unfractionated heparin is more frequently associated with osteoporosis, heparin-induced thrombocytopenia, and type I allergic reactions than LMWH.²⁶ Thus, unfractionated heparin should be reserved for women with a contraindication to LMWH (mostly chronic renal failure with a creatinine clearance below 30 mL/min) or when LMWH is not available.²⁶ Given the abovementioned disadvantages of unfractionated heparin, I prefer switching to vitamin K antagonists in the second trimester of pregnancy over unfractionated heparin subcutaneously throughout pregnancy.

Finally, in case of life-threatening pulmonary embolism, i.e. pregnant women with an established diagnosis who are hemodynamically unstable, systemic thrombolysis with either recombinant tissue plasminogen activator or streptokinase (whatever protocol is in place) is justified. In a recent review of 13 cases (with its obvious risk of publication bias), no maternal deaths occurred, at a maternal major bleeding risk of approximately 30%.³⁵

Management of delivery

Several options for delivery in women using anticoagulants are possible, and depend strongly on local preferences and experience, rather than evidence. A well-described plan, made by a multidisciplinary team, should be available. Several options are possible, including

spontaneous labor and delivery, induction of labor, and elective cesarean section. In our hospital, we have a monthly meeting with the obstetricians in which all anticoagulated pregnant women are discussed. If there is no obstetric indication for an induced delivery, we instruct women to not inject LMWH as soon as labour starts with either contractions or rupture of the membranes. We explain to women that they will not be able to receive neuraxial anesthesia, and that in case of an indication for anesthesia (which is not a routine procedure in the Netherlands), intramuscular or intravenous methods will have to be employed which may be less effective. In case of an emergency cesarean section, this will be done with general anesthesia. With this approach, most women will deliver within 24 hours, and with the peak antiXa level at 4 hours after the last injection, most women remain somewhat, but not fully anticoagulated while in labour. Active management of the third stage of labour is necessary to minimize the risks of obstetric hemorrhage. In women who are expected to deliver fast or have a history of peripartum bleeding, switching to a twice-daily regimen can be considered in the last weeks (e.g. from the gestational age of 37 weeks) prior to expected delivery.

When the level of anticoagulation is uncertain and where laboratory support allows for rapid assessment of heparin levels, then testing can be considered to guide anesthetic and surgical management, but in my experience this is very unpractical for antiXa levels. If bleeding occurs that is refractory to management of an obstetric cause, protamine sulfate may provide partial neutralization.

A planned delivery should be considered in women at very high risk for extension or recurrent VTE (arbitrarily within a month prior to expected delivery), so that the duration of time without anticoagulation can be minimized. Those at the highest risk of recurrence (proximal DVT or PE within two weeks prior to delivery) can be switched to therapeutic intravenous unfractionated heparin, which is then discontinued 4 hours prior to the expected time of

delivery or the use of neuraxial anesthesia.

In exceptional cases, for instance in such women who also have a contraindication to anticoagulation transiently (need for a cesarian section), the use of a temporary inferior vena cava filter may be considered. Still, experience with these devices during pregnancy is limited and filter migration and inferior caval vein perforation have been described in pregnant patients.^{52;53} Even in a large hospital like ours, with highly experienced interventional radiologists, their experience with filters in this population, and through the jugular route, is virtually absent.

Postpartum management

Anticoagulation should be restarted after delivery, as soon as possible, but depending on the amount of estimated vaginal blood loss and the type of delivery. Generally, restarting anticoagulation 6 to 12 hours after delivery is feasible, but this period should be longer if hemostasis is not adequate. I first restart LMWH, and initiate the first dose of vitamin K antagonists at least one day later. LMWH can be discontinued when the INR has been above 2.0 on at least two consecutive occasions. Alternatively, based on patients preference, continuation with therapeutic dose LMWH until 6 weeks postpartum (or until discontinuation if VTE occurred in late pregnancy) is an option. It is important to reassure women that they can breastfeed during use of either LMWH or vitamin K antagonists; particularly non-lipophilic types such as acenocoumarol and warfarin.^{54;55}

Conclusions

The management of pregnancy-related VTE is based on extrapolation from the non-pregnant

population and clinical trial data for the optimal treatment are not available. LMWH in therapeutic doses is the treatment of choice during pregnancy, and anticoagulation (LMWH or vitamin K antagonists postpartum) should be continued until 6 weeks after delivery with a minimum total duration of 3 months. Whether dosing should be based on weight or antiXa levels is unknown, and practices differ between centers. Management of delivery requires a multidisciplinary approach, and neuraxial anesthesia is generally contraindicated in obstetric patients who need therapeutic anticoagulation.

Authorship

S.M. is the sole author of the manuscript.

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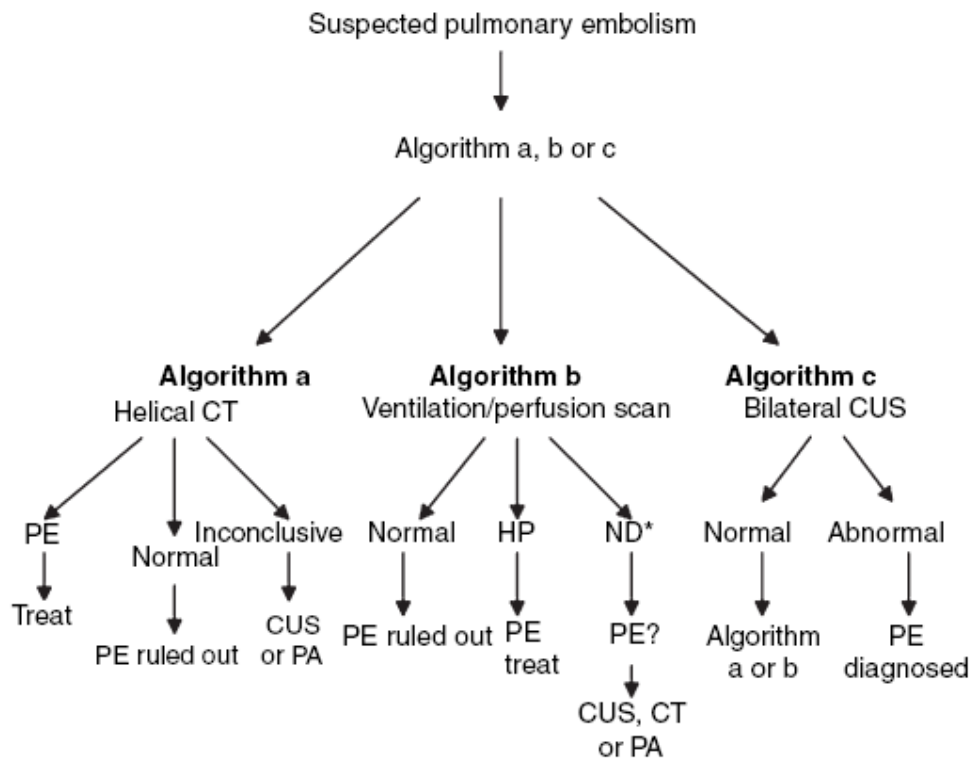
Table: How I treat pregnancy-related VTE, and a summary of alternatives*

	My approach in most patients	My alternatives (not exhaustive)
Diagnosis of suspected DVT or PE	<p>Imaging of proximal leg veins with compression ultrasound (CUS)</p> <p>If suspected PE, and CUS negative, spiral multi-slice detector CT scanning of the lungs</p>	<p>Immediate CT scanning of the lungs</p> <p>If suspected PE, algorithm of initial CUS, if negative V/Q scanning of the lungs, followed by pulmonary angiography if V/Q scan non-diagnostic</p>
Initial treatment of VTE in pregnancy	<p>Twice-daily therapeutic dose LMWH s.c. at a starting dose based on actual body weight; if uncomplicated, continuation with therapeutic dose LMWH in a once-daily regimen, based on actual body weight and peak antiXa levels 4 hours after injection (instruct women to inject LMWH in the morning).</p> <p>Infrequent monitoring of platelets and antiXa levels (every 6 to 8 weeks, combined with obstetric follow-up).</p> <p>Multidisciplinary plan for delivery. Counsel women about not being able to receive neuraxial anesthesia but alternative methods instead if necessary.</p>	<p>Continuation with twice-daily regimen of therapeutic dose LMWH, in women with increased bleeding risk or imminent delivery.</p> <p>Unfractionated heparin intravenously with close APTT monitoring, in women with increased bleeding risk or imminent delivery.</p> <p>Temporary vena cava filter in women with an absolute contraindication for anticoagulation.</p>
Management of delivery	<p>As soon as spontaneous labour starts, no LMWH injections. Avoid neuraxial</p>	<p>Switch to twice-daily regimen of therapeutic dose LMWH from gestational age of 37</p>

	<p>anesthesia. Active management of third stage of labour.</p>	<p>weeks, in women with increased bleeding risk.</p> <p>Planned delivery in women with recent VTE (4 weeks prior to expected delivery); consider switching LMWH to unfractionated heparin i.v. with APTT monitoring in women with acute VTE (i.e. in recent 2 weeks) who have to deliver. Stop unfractionated heparin 4 hours prior to delivery. Neuraxial anesthesia is possible. Consider temporary inferior vena cava filter.</p>
<p>Postpartum management</p>	<p>Restart LMWH 6 to 12 hours post delivery, depending on amount of blood loss and adequate hemostasis. Continue until INR is above 2.0 on two consecutive occasions.</p> <p>Start vitamin K antagonists one day after restarting LMWH if hemostasis is adequate.</p> <p>Breastfeeding is not contraindicated.</p> <p>Duration of anticoagulation until 6 weeks postpartum, or longer to guarantee a minimum total duration of 3 months if VTE occurred in late pregnancy.</p>	<p>Continue LMHW for the rest of the anticoagulation period, if preferred by the patient.</p>

* For justification, please see full text

Figure: Proposed algorithm in pregnant women with suspected pulmonary embolism



Abbreviations:

PE: pulmonary embolism

CUS: compression ultrasound

PA: pulmonary angiography

HP: high probability

ND: non-diagnostic

Adapted from Nijkeuter et al.¹¹