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REVIEW ARTICLE

Anticoagulant treatment of venous thromboembolism in pregnant women

Anetta Undas

Institute of Cardiology, Jagiellonian University Medical College, Kraków, Poland

Abstract

Venous thromboembolism (VTE), in particular pulmonary embolism (PE), remains the leading cause of death among pregnant women. Low-molecular-weight heparin (LMWH), with preference for therapeutic doses given twice daily according to European guidelines, is the drug of choice for the treatment of VTE in pregnancy and the puerperium. The recommended therapeutic dose is calculated on early pregnancy body weight. Evidence to support anti-Xa monitoring in pregnancy is weak. Unfractionated heparin (UFH) with multiple activated partial thromboplastin time measurements is still used in the acute treatment of high-risk PE. American experts have suggested considering initial outpatient therapy over hospital admission also in pregnant women with low-risk acute VTE, but European experts suggest adopting such a strategy selectively, for example in isolated distal leg thrombosis. Scheduled delivery with prior discontinuation of anticoagulant therapy in pregnant women who received a therapeutic dose of LMWH is suggested with the restart of therapy 4–6 h after a vaginal birth and 6–12 h after a cesarean delivery. It is recommended that UFH, LMWH, warfarin, acenocoumarol, or fondaparinux, but not direct-acting oral anticoagulants, should be used in breastfeeding women.

This review summarizes the key messages from current guidelines mainly based on low-quality evidence and expert consensus.

Key words: venous thromboembolism, pregnancy, anticoagulation

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Introduction

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs four or five times more frequently in pregnant women compared to nonpregnant women of a similar age. It is estimated that VTE occurs in 0.05–0.20% of all pregnancies [1–4], with predominance of DVT over PE [5, 6]. However, PE remains the leading cause of death among pregnant women, with mortality of about 4% [7]. The risk of VTE rises with each month of pregnancy, and peaks within the first two weeks after birth [5, 8], but increased risk is still seen during the first six post-partum weeks [1, 5, 8]. The incidence rate of VTE antepartum is estimated to be 118 [95% confidence interval [CI]: 101–137) per 100,000 person-years, and 424 (95% CI: 238–755) per 100,000 person-years postpartum [1–4]. The multiple mechanisms behind the elevated risk of VTE in pregnant women involve pelvic venous compression by the gravid uterus, venous stasis, compression of the left iliac vein by the right iliac artery, and prothrombotic alterations to blood coagulation including increased factor VIII, fibrinogen, thrombin generation and reduced free protein S, accompanied by enhanced platelet activation and hypofibrinolysis largely driven by elevated plasminogen activator inhibitor-1 (PAI-1) [1, 5, 8].

Address for correspondence: Anetta Undas, Institute of Cardiology, Jagiellonian University Medical College, Prądnicka 80, 31–202 Kraków, Poland, phone +48 12 614 30 04, fax +48 12 614 21 20, e-mail: mmundas@cyf-kr.edu.pl

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Risk factors and VTE prevention in pregnancy

It is recommended that women who plan pregnancy, or those in early pregnancy, should be assessed in terms of risk factors for VTE [9]. Women are classified to be at low, intermediate, or high risk of VTE, and prevention should be administered accordingly [9]. There is no established VTE risk assessment scoring system during pregnancy [10]. Recently, it has been demonstrated that infection, varicose veins, preeclampsia/eclampsia, emergency cesarean delivery, stillbirth, and medical comorbidities predict VTE after childbirth [11]. There is consensus that unprovoked VTE, hormone-related VTE, antiphospholipid syndrome, severe thrombophilia, and concomitant cancer represent high risk factors [12]. Approximately 6–12% of women who have experienced unprovoked or hormone-associated VTE in the past will suffer from VTE during pregnancy if thromboprophylaxis is not initiated, but the risk of recurrent episodes is still higher than in women without such previous events [13, 14]. It has been suggested that thromboprophylaxis during pregnancy should be initiated if the estimated VTE risk is approximately 2% [10]. Thrombophilia-associated VTE risk is highly heterogenous in pregnancy. In young women heterozygous for the factor V Leiden (FVL) polymorphism, the risk is about 0.5%, while in those with heterozygosity for both FVL and the prothrombin gene *G20210A* polymorphism, the risk is much higher, c.5.5%. In antithrombin (type I) deficient women, it is 11.6% during pregnancy without thromboprophylaxis [10].

A 2014 Cochrane systematic review of randomized trials led to the conclusion that "there is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy (and that) large scale, high–quality randomized trials of currently used interventions are warranted" [15].

Prospective studies have however indicated that thromboprophylaxis can reduce VTE risk in pregnancy from 2.4–12.2% in its absence to 0.5–5.5% observed in women on heparin-based prevention [14, 16].

For many years, low-molecular-weight heparin (LMWH; in Poland enoxaparin, dalteparin, and nadroparin) has been the drug of choice for the prevention and treatment of VTE in pregnant women [17]. Preventive strategies are based on expert opinion and low–quality evidence, and therefore pharmacological thromboprophylaxis should be used wisely, taking into account commonly reported easy bruising, minor bleeding, skin allergic reactions (about 2%), pain, bone loss, heparin-induced thrombocytopenia (in <0.5%) and also high out–of–pocket costs for pregnant women. The initial dose of LMWH for thromboprophylaxis should be based on body weight in early pregnancy, i.e. 8–10 weeks [18]. Consequently, patients at high risk for VTE should receive LMWH i.e. enoxaparin at 0.5 IU/kg of body weight once daily [18] or at equivalent doses. In obese women (>100–120 kg), weight-based dosing (enoxaparin 40 mg bid) is commonly recommended based on the concept that the daily dose should be high enough to achieve adequate anti-Xa activity estimated at 0.2–0.6 IU/mL [19]. Despite controversy surrounding the optimal thromboprophylaxis in pregnancy, there is consensus that pregnant women with prior VTE who are not receiving anticoagulation should receive six weeks of postpartum prophylaxis. Importantly, experts underscore that all pregnant women at risk of VTE should be educated as to its signs and symptoms and the need to consult a physician if they develop [20].

Diagnosis of acute VTE in pregnancy

Dyspnea, poor exercise tolerance, pleuritic chest pain, cough, tachycardia, tachypnea, and hemoptysis represent the common symptoms and signs of PE during pregnancy that are identical to those observed in other PE patients. In the case of suspected DVT, physicians should pay attention to unilateral leg edema and increased swelling of one leg, in particular the left. In >85% of pregnant women with DVT, the veins of the left lower extremity are affected at least in part due to compression of the left iliac vein by both the left iliac artery and the gravid uterus. Persistent pain in the buttock, groin, flank, or even abdomen, can herald iliac vein thrombosis which is relatively common in pregnancy and associated with a 50% risk of subsequent acute PE.

Compression ultrasound is the diagnostic imaging procedure of choice for suspected DVT in pregnancy, with a high sensitivity and specificity for proximal DVT [12]. It has been proposed that the absence of the three following features: left leg presentation, >2 cm calf circumference difference, and first trimester, has a nearly 100% negative predictive value in the diagnosis of iliac vein thrombosis if ultrasonography of the leg veins does not detect thrombosis [21]. Its value is much lower in the detection of either distal DVT or pelvic DVT compared to proximal DVT, which is of particular importance in pregnancy. Serial compression ultrasound imaging on days 0, 3, and 7 in pregnant women has been reported to have almost 100% negative predictive value, which allows the exclusion of DVT [22]. If the initial compression ultrasound is negative, then MRI venography may be considered to exclude a pelvic DVT, but not DVT at other locations [22]. If the clinical suspicion is high, the use of heparin should be initiated and compression ultrasonography should be repeated on days 3 and 7. If the initial clinical suspicion is low, then anticoagulation can be stopped after a negative result of compression ultrasonography, but repeat imaging should be performed on days 3 and 7 [22]. If such a strategy is unfeasible in practice, heparin administration should be continued with clinical evaluation of symptoms and signs.

In pregnant women, clinical prediction scores for assigning pre-test probabilities of VTE and diagnostic algorithms used in patients suspected of PE have not been validated [23]. Given the risk of death, all pregnant women in whom acute PE is suspected should be assessed and therapeutic anticoagulation should be initiated until the diagnosis is made.

Interpretation of D-dimer concentrations in pregnant women is challenging. It is well known that D-dimer levels rise in each pregnancy and each trimester. It has been estimated that there is a 39% relative increase in D-dimer concentration for each trimester [24]. A positive D-dimer test, defined as a D-dimer concentration of above 500 ng/mL, in pregnant women is not necessarily a marker of developing acute VTE, while normal D-dimer concentrations have been observed despite objective confirmation of acute VTE by imaging [25]. Imaging is needed to confirm or refute the suspicion of VTE in this clinical setting [26].

There is no consensus on the best diagnostic strategy for pregnant women suspected of acute PE [27]. A modified Wells score has been suggested to be used in combination with D-dimer measurement to identify pregnant women who require imaging [28, 29].

If the index of suspicion of DVT remains high, then compression USG should be performed. If this is abnormal, then anticoagulation is indicated. If compression USG is negative, then further testing is required and MRI should be performed. Where PE is suspected and all other investigations are being normal, low-dose CT should be undertaken [12].

Treatment of acute VTE in pregnancy

LMWH is the drug of choice for the treatment of VTE in pregnancy and the puerperium. In acute VTE, treatment with therapeutic doses of weight-adjusted LMWH should be given twice daily according to the European guidelines on the management of PE [12].

The American Society of Hematology (ASH) guidelines panel strongly recommends therapy with LMWH over unfractionated heparin (UFH) in pregnant women in whom acute VTE has been diagnosed, with no clear preference for either once-per-day or twice-per-day dosing regimens given the limited evidence to support one of these two options in practice [30].

In a systematic review and meta-analysis, treatment of pregnancy-associated VTE with LMWH or UFH led to an estimated antepartum mean VTE recurrence incidence of 1.97% (95% CI: 0.88–3.49), accompanied by a risk of major bleeding of 1.41% (95% CI: 0.62–2.41%) prior to delivery and of 1.20% (95% CI: 0.3–2.50%) during the 24 h after delivery [31]. The results of two meta-analyses of studies performed on a nonpregnant population showed that the risks of bleeding occurring during the initial therapy of acute VTE with LMWH and UFH did not differ [32, 33]. Pregnant women on heparin therapy are most likely exposed to the same risks while on LMWH or UFH.

As in the non-pregnant population, it is strongly recommended that in all subjects with suspected DVT or PE, therapeutic LMWH should be given until the diagnosis has been excluded by objective testing [32–34]. Anticoagulation is very effective in decreasing the risk of PE-related death. Therefore, pregnant women especially should not be sent to other specialists for further tests or to hospital if the appropriate therapy has not been initiated.

The recommended therapeutic dose is calculated on early pregnancy body weight (i.e. enoxaparin 1 mg/kg body weight twice daily or dalteparin 100 IU/kg body weight twice daily) [34]. The target peak anti-Xa values, typically determined 4–6 h after injection, range from 0.6 to 1.2 IU/mL [34]. However, evidence to support anti-Xa monitoring is weak. Some, but not all, observational studies have reported a need for dose adjustments when anti-Xa levels have been used to guide therapy [35–41]. However, none demonstrated a clear clinical benefit from the LMWH dose adjustments e.g. reduced blood loss at the time of delivery in women with FXa monitoring [42]. Given the available evidence, the risk and benefits related to anti-FXa monitoring in pregnant women are probably small. With regard to the risk of thrombocytopenia in heparin-treated women, experts in Canada have suggested assessing platelet count seven days after the start of therapy. However, the risk of clinically relevant thrombocytopenia while on LMWH in pregnancy is 0.1–0.2%, and therefore this approach is rarely used in practice if pregnant women are treated exclusively with LMWH [20].

UFH intravenous (i.v.) with multiple activated partial thromboplastin time (APTT) measurements is used in the acute treatment of high-risk PE.

Thrombolytic therapy, in most cases with alteplase i.v., should only be used in acute PE patients with severe hypotension or shock [43]. Following thrombolysis, UFH should be started at a rate of 18 U/kg/h without administration of the loading dose and initiation of therapeutic-dose LMWH as soon as stabilization has been achieved [12]. Thrombolysis is rarely used in limb-threatening DVT in pregnancy [20].

Fondaparinux (7.5 mg once a day in normal weight or 10 mg if weight exceeds 100 kg) can be considered if LMWH is not well tolerated or causes adverse events e.g. skin allergy or if heparin-induced thrombocytopenia develops, or also if this life-threatening adverse event is even only suspected based on a drop in platelet count by 50% or more, usually after 5–15 days of therapy.

The insertion of vena cava filters is not recommended in most cases of massive proximal DVT with PE, since the procedure is associated with several risks, in particular if the presence of a filter is prolonged [43, 44]. In some centers, a temporary vena cava filter is inserted prior to planned

delivery in women at highest risk of fatal PE, in particular those who developed proximal DVT (i.e. iliac vein thrombosis) or massive PE within the 2–4 preceding weeks, in particular in the presence of contraindications to anticoagulation (e.g. intracranial bleeding). The filter should be removed a few weeks postpartum [20].

Importantly, the ASH panel advises against the addition of catheter-directed thrombolysis therapy to anticoagulation in pregnant women who develop both massive proximal DVT and/or acute PE with right ventricular dysfunction in the absence of hemodynamic instability [30]. In the case of hemodynamic instability, the panel suggests administering systemic thrombolytic therapy in addition to anticoagulant therapy [30]. To date, there have been two analyses of observational studies in which the efficacy and safety of systemic thrombolysis in a total of 31 pregnant women were evaluated; they demonstrated five neonatal deaths not related to bleeding or thrombolytic therapy, with no cases of maternal death [45, 46].

American experts suggest considering initial outpatient therapy over hospital admission also in pregnant women with low-risk acute VTE [30]. European experts however suggest adopting such a strategy only in certain circumstances, for example in isolated distal DVT or popliteal vein DVT in young patients free of other conditions increasing morbidity e.g. diabetes.

Anticoagulation and delivery

In women on therapeutic LMWH, delivery should be planned at a maximum of 39 weeks to minimize the possibility of unexpected labor following the administration of full-dose heparin, as protamine sulfate can reverse 50% of anticoagulant effects of LMWH, which might lead to major bleeding. Whether to stop anticoagulation before delivery depends on the VTE risk. In high-risk women on therapeutic LMWH, LMWH should be withdrawn and replaced by i.v. UFH at least 36 h prior to delivery, and the infusion of UFH should be stopped 4–6 h prior to anticipated delivery. Normal APTT, determined after 4–6 h, is needed to decide on the use of regional anesthesia.

In contrast, if the VTE risk is low in women on therapeutic LMWH or those on thromboprophylaxis with a higher-than-standard dose administered twice daily, the evening dose of LMWH should be omitted and induction of delivery or cesarean section performed the next morning, with regional anesthesia started more than 24 h after the last dose of LMWH and if no antithrombotic agents e.g. aspirin are used [47]. In the case of therapeutic anticoagulation prior to delivery, and if neuroaxial anesthesia was used, monitoring for the development of spinal hematoma should be carried out.

In women who received therapeutic-dose heparin before delivery, European experts recommend (to decrease the risk of postpartum major bleeding) that in the third stage of labor a modified dose of oxytocin should be administered, namely 2 IU oxytocin over 5 min added to a standard infusion for 4 h [10 U of oxytocin in 500 mL of normal saline given i.v. at 36 mL/h for 4 h (12 mU/min)], as such a protocol has been demonstrated to reduce blood loss [47].

In women with VTE who received heparin therapy prior to childbirth, the treatment should be restarted 4–6 h after a vaginal birth and 6–12 h after a cesarean delivery unless major bleeding has occurred. Some experts from the United Kingdom suggest initiating VKA at least five days after delivery, which is common practice. The overlap of LMWH with VKAs for at least five days should be recommended, then LMWH withdrawn and VKA continued for at least three months, or six months if PE was diagnosed in the third trimester. The target INR is 2–3 and its determination should be performed every 1–2 weeks. In women who preferred LMWH over the entire period of postpartum anticoagulant treatment, parenteral therapy could be continued ideally once a day without any anti-Xa measurements [12].

The ASH guideline panel suggests scheduled delivery with prior discontinuation of anticoagulant therapy in pregnant women who received therapeutic dose LMWH and "against scheduled delivery with discontinuation of prophylactic anticoagulation compared to allowing spontaneous labor" if a prophylactic dose of LMWH was administered [30].

Anticoagulant use in breastfeeding women

The ASH panel recommends in favor of using UFH, LMWH, warfarin, acenocoumarol, or fondaparinux in breastfeeding women, and recommends against using direct oral anticoagulatns (DOACs) [30].

UFH is not excreted to breast milk due to its large size and negative charge [48], while LMWH can be found in breast milk at negligible levels based on the measurement of anti-FXa activity (below 0.04 IU/mL) in treated women [49], with no risk of clinically relevant bleeding in the infant. Vitamin K antagonists are nonlipophilic and highly protein bound and are not excreted into breast milk [50]. There is no published data on the excretion of fondaparinux into breast milk, but orally taken heparins have low availability [49]. Although it has been reported that rivaroxaban is detectable in breast milk at very low levels [51], DOACs are strongly contraindicated in breastfeeding women, as in pregnancy.

Conclusions

Anticoagulation in pregnant women with VTE is challenging and based mainly on low-quality evidence. The prompt initiation of LMWH therapy with its continuation up to six weeks after delivery is the cornerstone of anticoagulant strategy, which is effective in reducing the risk of life-threatening PE. The decision as to how long anticoagulation should be administered after pregnancy-related VTE should be individualized.

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AU — sole author.

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Ethics
The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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