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The prevention and treatment of venous thromboembolism in pregnancy

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Abstract

Introduction: Venous thromboembolism (VTE) in pregnancy represents an important cause of maternal morbidity and mortality in developed countries, with an incidence of 0.5-2.2 per 1000 pregnancies. In addition to haemostatic occurring during normal pregnancy, several risk factors have been identified. Thus, a variety of clinical conditions as well as fetal and maternal risks linked to a possible anticoagulant therapy should be considered for the management of VTE during pregnancy. Unfortunately, there is a paucity of high-quality evidence from randomized trials in this field, and current recommendations are based on observational studies or evidence gathered from studies in the non-pregnant population.

Areas covered: The purpose of this review is to summarize available evidence on the prevention and treatment of pregnancy-related VTE.

Expert commentary: Although the optimal prophylactic and therapeutic dosage has not yet been established, low-molecular-weight heparin (LMWH) represents the most efficacious and safe anticoagulant during pregnancy. Thus, after an accurate risk stratification of women during pregnancy and puerperium, LMWH should be recommended to women at risk for VTE and to those ones suffering from an acute event.

Keywords: Heparin, Postpartum period, Pregnancy, Venous thromboembolism, Thromboprophylaxis
1. Introduction

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep-vein thrombosis (DVT), affects up to 0.5-2.2 per 1000 pregnancies. [1-8] Although rare in absolute terms, VTE represents an important cause of morbidity and mortality in obstetric populations from Western countries. [9]

It has been estimated that, during pregnancy, the risk of VTE is increased 5 to 10-fold compared to age-matched non-pregnant women; this risk is particularly relevant during the postpartum period. [1,7,10,11] More recently, an increased VTE risk in pregnancies after Assisted Reproductive Technologies (ART) compared to the spontaneous ones has been suggested by several observational studies. [12-15] In these women, ovarian hyperstimulation syndrome (OHSS) represents the main factor involved in the VTE occurrence, with a 100-fold increased risk. [12,16]

However, in addition to pregnancy itself or related conditions, risk factors for VTE include inherited (factor V Leiden, FIIA20210 prothrombin mutation, and deficiencies in protein S and C and antithrombin) and acquired (confirmed presence of antiphospholipid antibodies) thrombophilias, personal and family history of VTE, smoking, age greater than 35 years, obesity, immobilization, co-existing medical morbidities. [3,5,17-19] Very recently, in women with severe thrombophilia a high absolute risk of pregnancy-related VTE independent of a positive family history of VTE has been reported. [20] Thus, a variety of clinical situations should be considered and a personalized clinical approach given to all women referred for the management of VTE during pregnancy. Unfortunately, there is a paucity of high-quality evidence from randomized trials in the field of women’s issues in thrombosis and haemostasis, and current recommendations are based on observational studies or evidence gathered from studies in the non-pregnant population.

The purpose of this review is to summarize available evidence on the prevention and treatment of pregnancy-related VTE.

2. Hemostatic changes in normal pregnancy
Normal pregnancy is accompanied by changes in the coagulation and fibrinolytic systems all contributing to maintain placental function during pregnancy and to prevent excessive bleeding in delivery. [21] These include a decrease in platelet count, an increase in coagulation factors, a decrease in natural anticoagulants, a significant fall in the activity of activated protein C and inhibition of fibrinolysis. These changes may be important for reducing intrapartum blood loss, but they determine an increased risk of VTE during pregnancy and puerperium. [22] In addition, reduction in venous flow velocity in late pregnancy,[23,24] due to the vasodilatory effects of pregnancy hormones and physical obstruction from the gravid uterus, may further predispose pregnant women to VTE. In this scenario, anticoagulation could give benefit to women at higher risk of VTE.

3. Anticoagulation during pregnancy

Prevention and treatment of VTE during pregnancy and postpartum period should take into account fetal risks linked to a possible anticoagulant therapy, as well as maternal efficacy and safety.

Oral anticoagulation with vitamin K antagonists crosses the placenta and can cause teratogenicity as well as pregnancy loss, fetal and maternal bleeding, and neurodevelopmental deficits. [25-28] Although more recent prospective studies report a lower risk for coumarin embryopathy[29], in general their use is contraindicated in pregnancy except in high-risk cases, such as women with artificial heart valves, in whom they have been used after embryogenesis in the first trimester. The newer direct oral anticoagulants, such as dabigatran, rivaroxaban, apixaban, and edoxaban, may also cross the placenta and should generally be avoided in pregnancy. [30] However, no embryotoxic risk in women inadvertently exposed to rivaroxaban during early pregnancy has been recently reported by the German Embryotox Pharmacovigilance Centre. [31]

Fondaparinux appears to cross the placenta in small quantities, [32] but it is generally only prescribed in cases of severe heparin allergy or heparin induced thrombocytopenia (HIT). [30]
Low-molecular-weight heparin (LMWH), as well as unfractionated heparin (UFH), do not cross the placenta [33] and, therefore, are safe for the fetus. However, compared with UFH, LMWH has a better bioavailability, longer plasma half-life, more predictable dose response, and improved safety profile with respect to osteoporosis and HIT [30]. Thus, LMWHs represent the anticoagulant of choice for VTE prophylaxis and treatment in pregnancy, with a clear consensus amongst the reviewed guideline documents [34].

Women receiving anticoagulants need an individualized delivery plan to avoid the risk of haemorrhage in women on full therapeutic anticoagulation or the risk of VTE when treatment is discontinued during the induction and/or labour period. In general, spontaneous labour is preferable in women on treatment. In this situation, heparin should be discontinued once there are signs of labour. If there is a planned delivery, prophylactic and therapeutic LMWH should be discontinued at least 10-12 h and 24 h prior epidural analgesia/delivery and restarted 6-12 h and 24 h after delivery, respectively [34].

As far as the breastfeeding phase is concerned, LMWH as well as UFH and oral anticoagulants (except the new ones) have proven safety in breast feeding women, due to their limited transfer into breast milk.

4. Prevention of pregnancy-related VTE

Antithrombotic drugs, such as heparin or low dose aspirin, are extensively used in pregnant women with previous gestational vascular complications (GVS) to improve pregnancy outcome. In general, heparin is suggested in women with previous late GVCs, aspirin in women at risk for pre-eclampsia or antiphospholipid antibodies syndrome [35]. The rationale for their use is the thrombotic or inflammatory process involved in these complications [36]. However, available evidence is very limited and no definitive conclusions can be drawn. It has been suggested that heparin, in particular LMWH, could also improve clinical pregnancy and live birth rates in women undergoing ART [37-40]. However, not enough data are available regarding prophylaxis with heparins to prevent
pregnancy-related VTE. A recent Cochrane review has assessed the effects of thromboprophylaxis on the VTE incidence during pregnancy or puerperium. Sixteen controlled trials with 2592 women have been examined but no reduction in the risk of maternal death, DVT, or PE, was found and no differences were shown for these outcomes when different types of heparin were compared. [41] The insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period are dependent mainly on the low methodological quality of trials to date performed. Finally, a review on thromboprophylaxis and treatment of pregnancy-related VTE based on existing guidelines and available literature has been recently published. The authors of this review recommend that high-risk patients should be offered thromboprophylaxis. [34] Therefore, a careful evaluation of all known pre-existing and pregnancy-related risk factors in both antepartum and postpartum periods is crucial to identify moderate-/high-risk women who could benefit antithrombotic prophylaxis. The RCOG guidelines on antenatal and postnatal thromboprophylaxis according to the level of risk are summarized in Table 1. In any case, if the decision is made to use antepartum prophylaxis, it should be instituted from the earliest possible stages of pregnancy, due to early activation of the haemostatic system. [42,43] Similarly, as the VTE risk is increased during the first 3-6 weeks postpartum, [1,7] prophylaxis should be extended until 6 weeks after delivery. [44-46,30] Although LMWHs represent the anticoagulant of choice for VTE prophylaxis in pregnancy, [34] optimal dosage and molecules to be used or the weight of each risk factor in predicting the recurrence are not still available in the literature and some failures of LMWH prophylaxis have been reported. [47-50] However, an ongoing randomized-controlled trial comparing two different doses of LMWH in pregnant patients with a history of previous VTE could probably help clinicians in the choice of dosing strategies efficacious in preventing recurrent VTE in pregnancy (Highlow Randomized Controlled Trial; NCT001828697). In any case, an individualized risk benefit assessment of prophylaxis, as well as women’s participation in shared decision-making regarding their management should be adopted.
Mechanical prophylaxis with elastic stockings and/or intermittent pneumatic compression is an alternative for hospitalized women with contraindications to anticoagulant prophylaxis. However, there is limited evidence about their efficacy. [30]

A particular area where thromboprophylaxis is often not considered is assisted reproduction. In women undergoing ART, thromboprophylaxis with LMWH is recommended only to those ones who develop severe OHSS for 3 months after OHSS resolution. [30] However, in pregnancies after ART a higher risk of VTE has been recently reported, independently of the OHSS occurrence. [12-15] Therefore, other risk factors should probably be considered for thromboprophylaxis. In fact, these women often show the coexistence of multiple risk factors, such as age over 35 years in addition to ovarian stimulation.

Last but not least, women’s education on signs and symptoms of DVT and PE is important in order to promptly provide adequate interventions and, therefore, to prevent fatal complications.

5. Treatment of pregnancy-related VTE

Treatment of VTE in pregnancy involves LMWH as well, usually for a minimum total duration of 3 months and until at least 6 weeks postpartum. However, given the increased risk of VTE during the whole pregnancy, available guidelines suggest therapeutic doses of LMWH throughout the remainder of the pregnancy. [45,46,30,51-53] On the contrary, it is not yet established whether the dose of LMWH can be reduced to an intermediate dose after an initial period of treatment. [46] A dose reduction strategy (75% of a full treatment dose) after at least a month of therapy has been suggested by some guidelines only for women at risk for bleeding or osteoporosis. [30]

A recent systematic review and meta-analysis of the literature evaluating the risk of bleeding and VTE recurrence in women with acute VTE during pregnancy treated with antithrombotic therapy (LMWH or UFH) reassures about their safety and efficacy, with a reported incidence of major bleeding of 1.41% (95% CI 0.60-2.41%; I) and 1.90% (95% CI 0.80-3.60%) before and after delivery, respectively, and an incidence of VTE recurrence of 1.97% (95% CI 0.88-3.49%; I(2)
Nevertheless, the risk of VTE recurrence or bleeding cannot be entirely excluded, and a periodic clinical surveillance should be guaranteed to these women, especially around the time of delivery.

Although LMWHs are safe during pregnancy, there are no large trials examining their optimal therapeutic dosage. Thus, different therapeutic strategies are currently used in clinical practice. Some studies suggest LMWH dose-adjustment over the course of pregnancy according to anti-Xa levels [54,55] or increasing weight; [56] others recommend a twice-daily LMWH dosing schedule to compensate for increases renal clearance of this medication that occur during the second trimester. However, available evidence on this issue is conflicting; no benefit of dose-adjustment, [57-61] as well as difference in the risk of recurrence with a once-daily regimen compared with twice-daily schedules [62,63] has been demonstrated by other studies. Thus, clinicians’ choice is based on their own clinical experience with once- or twice-daily regimen. Routine monitoring of anti-Xa levels is not currently recommended, probably due to the lack of an optimal therapeutic anti-Xa LMWH range. However, it could be helpful in particular clinical conditions, such as extreme levels of body weight (less than 50 kg or greater than 90 kg), and in women with complicating factors such as renal disease and recurrent VTE despite appropriate treatment. [46]

Graduated elastic compression stockings reduce pain and swelling in patients with acute DVT, with no increased risk of clot progression and subsequent pulmonary embolism. However, it cannot be advocated for prevention of post thrombotic syndrome.

6. Conclusion
Prevention and treatment of VTE in the obstetric population is challenging because of the need to consider and preserve fetal and maternal well-being. In addition, current available recommendations are inconsistent and low-quality, being based largely upon observational studies or evidence gathered from studies in the non-pregnant population. Further studies to better explore the optimal
prophylactic and therapeutic strategies according to risk stratification of obstetric populations are needed.

7. Expert Commentary

Women are at increased risk of VTE during pregnancy and the postpartum period. Although LMWH represents the most efficacious and safe anticoagulant, the optimal prophylactic and therapeutic dosage according to an accurate risk stratification of women has not been established, and the value of monitoring LMWH activity (anti Xa activity), has not been determined. These and other important gaps suggest that additional evidence obtained from adequately powered randomised controlled trials (RCTs) in the pregnant population is needed. On the other hand, it should be considered that previous attempts to carry out RCTs in obstetric population were unsuccessful, due to the high numbers of patients needed to enrol for obtaining significant differences and a slow rate of recruitment. Therefore, ad hoc observational studies could be an alternative to RCTs, by systematically registering who is treated, how long, and which doses are used. We are confident that two ongoing registers, primarily evaluating pregnancy outcomes in women with previous recurrent pregnancy loss and/or IUFD (OTTILIA, NCT02385461) and ART outcomes in women with previous ART failures (The FIRST Registry, NCT02685800) will also provide additional information on the risk and management of VTE. The prevention and treatment of VTE in the ART field is another challenging topic, due to the recently evidence of increased VTE risk in pregnancies after ART as compared to the spontaneous ones.

In any case, we must take into account that pregnancy-related VTE is still one of the most important causes of mortality of women during reproductive age. Thus, after an accurate risk stratification of women during pregnancy and puerperium, we recommend prophylaxis with LMWH in at-risk women.

8. Five-year view
Current strategies for prevention and treatment of pregnancy-related VTE are mainly based on inconsistent and low-quality evidence. However, although it is difficult to carry out RCTs in obstetric populations, we believe that findings from ad hoc observational studies and the choice of a personalized clinical approach according to an accurate risk stratification of women will allow to adequately manage pregnancy-related VTE in the near future.

9. Key issues

• Venous thromboembolism in pregnancy represents one of the most important cause of maternal morbidity and mortality in developed countries, with an incidence of 0.5-2.2 per 1000 pregnancies.

• Several factors are potentially involved in the VTE occurrence, in addition to pregnancy itself.

• Prevention and treatment of pregnancy-related VTE is challenging because of the need to consider and preserve fetal and maternal well-being.

• Current available recommendations for prevention and treatment of pregnancy-related VTE are largely based upon observational studies or evidence gathered from studies in the non-pregnant population.

• Although the optimal prophylactic and therapeutic dosage has not yet been established, low-molecular-weight heparin represents the most efficacious and safe anticoagulant during pregnancy.

• Unfortunately, prophylactic and therapeutic strategies currently used in clinical practice are often based on clinicians’ experience rather than evidence-based medicine, due to the lack of high-quality evidence from medical literature.
• Further studies to better explore the optimal prophylactic and therapeutic strategies according to risk stratification of obstetric populations are needed.

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Declaration of interest

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References


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<th>Table 1. VTE risk assessment and management</th>
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<td><strong>Pre-existing risk factors</strong></td>
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<td>Age &gt; 35 years</td>
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<tr>
<td>Obesity (BMI ≥ 30 Kg/m²)</td>
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<td>Parity ≥ 3</td>
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<td>Smoking</td>
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<td>Immobility</td>
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<td>Family history for VTE</td>
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<td>Pre-eclampsia in current pregnancy</td>
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<td>Preterm birth in current pregnancy (&lt;37 weeks)</td>
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<tr>
<td>Stillbirth in current pregnancy</td>
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<td>Prolonged labour (&gt;24 hours)</td>
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<td>Operative delivery/Caesarean section</td>
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<td>Postpartum Haemorrhage</td>
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<td>Antenatal prophylaxis: ≥ 3 risk factors</td>
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<td>Postnatal prophylaxis: ≥ 2 risk factors</td>
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FVL: factor V Leiden; PTm: prothrombin G20210A mutation; Severe thrombophilia: homozygosis for FVL or PTm, double mutation, FVL or PTm and/or natural anticoagulants deficiency.