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Chapter 2

Risk Factors, Treatment and Prevention of Venous Thromboembolism During Pregnancy and Postpartum

Roza Chaireti and Katarina Bremme

Additional information is available at the end of the chapter

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Abstract

The naturally hypercoagulable state occurring during pregnancy and anatomical changes and changes in the plasma volume are the main reasons for the increased risk of venous thromboembolism (VTE) during pregnancy and puerperium. This risk is particularly enhanced in the presence of thrombophilia and a previous history of VTE. The cornerstone for treating and preventing VTE is low molecular weight heparin (LMWH). There is currently no consensus on the dosing and the need for monitoring treatment with LMWH, and varying protocols are used in different clinics. The risk models used to stratify the risk for recurrence are based on the presence of factors such as previous VTE, familial history and thrombophilia and lead to decisions on the dosing and the duration of thromboprophylaxis. Treatment with LMWH is considered safe and effective, with low incidence of adverse effects (bleeding, osteoporosis, etc.) and recurrence of VTE. The use of direct oral anticoagulants is currently not recommended in this setting, but case series have not indicated increased embryopathy. The lack of international guidelines and large studies underlines the need for collaboration in order to further improve outcomes and patient safety.

Keywords: pregnancy, postpartum, thromboembolism, anticoagulation, thromboprophylaxis

1. Introduction: venous thromboembolism

Venous thromboembolism (VTE) is a relatively common disease with an incidence of 104–183 per 100,000 person-years among persons of European ancestry [1]. The clinical manifestations of VTE are pulmonary embolism (PE) and deep vein thrombosis (DVT), which is most often located in the lower extremities [2]. The incidence for PE and DVT ranges from 29 to 78 and 45

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to 117 per 100,000 person-years, respectively [3, 4]. VTE is associated with significant mortality and morbidity. Sudden death is the initial manifestation for about 25% of patients with PE [5], and PE is an independent marker for reduced survival early after its debut [6, 7]. Around 20–50% of patients with DVT will develop post-thrombotic syndrome [8] with the symptoms varying from mild pain and swelling to severe venous insufficiency and ulcerations [9, 10]. About 5% of the patients with PE can develop chronic thromboembolic pulmonary hypertension, leading to reduced lung capacity and heart failure [11].

The pathophysiology of VTE is complicated and will not be reviewed here. The basic mechanism behind the pathogenesis of VTE is likely attributed to the so-called Virchow's triad: (i) changes in blood flow (i.e. stasis), (ii) vascular endothelial injury and (iii) changes in blood components (i.e. inherited or acquired hypercoagulable states, thrombophilia) [12].

Venous thromboembolism is a multifactorial disease. The risk for VTE increases in the presence of acquired and inherited risk factors, such as thrombophilia [13], immobilization, trauma, recent surgery, cancer, etc. [14, 15]. Additionally, the female sex hormones, predominantly oestrogen, affect the coagulation cascade, tipping it towards hypercoagulability and therefore increasing the risk for thrombosis [16]. For example, the use of combined oral contraceptives [17] and hormone replacement therapy [18] are well-established risk factors for venous thrombosis, especially if other risk factors are present. Pregnancy is a naturally hypercoagulable state, and the risk for thrombosis is increased throughout pregnancy and persisting through puerperium [19, 20]. VTE is the seventh leading cause of maternal morbidity and mortality in Western countries [21, 22], accounting for ca. 10% of all maternal deaths [23]. Considering the burden of the disease and its impact on maternal and foetal health, it is imperative to early recognize and effectively treat venous thrombosis during pregnancy and postpartum. In this chapter, we describe the mechanisms behind the increased thrombotic risk during that period, as well as the principles of treatment and prevention of VTE.

2. Risk factors for venous thromboembolism

2.1. Pregnancy as a hypercoagulable state

During pregnancy, the coagulation balance leans towards hypercoagulability, as a means to protect the woman from fatal bleeding in the case of a miscarriage and during labour. This is mediated mainly by an increase in most procoagulant factors and a decrease in some anticoagulant factors, as well as a decrease in fibrinolytic activity [24].

The levels of fibrinogen begin to increase during the first trimester, reaching profoundly high levels during late pregnancy [25]. Along with fibrinogen, coagulation factors II, VII, VIII, X, XII and XIII increase by 20–200% during pregnancy [26]. Factors V and IX are slightly increased during normal pregnancy or unchanged according to some studies [25, 26]. Factor XIII increases at the beginning of pregnancy and decreases gradually afterwards, reaching levels about 50% of the normal non-pregnant value at term [25]. Factor XI is the only coagulation factor that decreases during pregnancy, with average values at about 60–70% of its normal

value (non-pregnant) [25, 27]. Von Willebrand factor increases during pregnancy. During the first half of the pregnancy, it follows the increase in factor VIII, but thereafter increases disproportionally, increasing the ratio of von Willebrand factor antigen to factor VIII coagulant activity from one to about two [25, 28]. Tissue factor does not change during pregnancy [29]. The anticoagulant protein S decreases during pregnancy; this decrease is particularly evident when measuring free protein S and less evident when measuring total protein S. The decrease in protein S persists up to at least 8 weeks postpartum [30]. Protein C remains unchanged [31], but pregnancy induces acquired activated protein C (APC) resistance [32]. Antithrombin values have previously been regarded as virtually unchanged, but later studies have shown that they fall to a level of about 20% of baseline levels [33]. Following partus, antithrombin levels fall additionally to 30% below baseline, with the lowest levels noted 12 hours postpartum, and return to normal about 3 days after birth [34, 35]. Tissue factor pathway inhibitor and thrombomodulin increase during pregnancy [36, 37].

Pregnancy is characterized by hypofibrinolysis. Fibrinolytic inhibitors such as thrombin activatable fibrinolysis inhibitor (TAFI) and plasminogen activator inhibitor-1 (PAI-1), and PAI-2, which is practically non-existent outside of pregnancy, increase [38]. In particular, PAI-1 levels increase significantly due to production from endothelial cells of the placenta and decidua [27, 30].

Plasminogen and tissue-type plasminogen activator increase [39]. The urokinase-type plasminogen activator is also increased during normal pregnancy [40]. Thrombin cleavage products such as D-dimer and fibrin monomers increase, suggesting ongoing and active coagulation [41, 42].

Platelet counts remain within the range of normal values in most pregnancies but can be lower in about 5% of pregnancies (gestational thrombocytopenia) [43, 44], whereas the mean platelet volume is unchanged [45] or increased [46]. Gestational thrombocytopenia is usually mild and occurs during the third trimester. It resolves spontaneously following delivery and platelet counts continue to increase for the first 3–4 weeks postpartum as a marker for increased inflammatory activity. Thereafter, platelet counts return to normal values [47]. Although increased platelet aggregation has been reported during pregnancy [48], the issue of increased platelet activation in an uncomplicated pregnancy is still controversial [49, 50].

Following delivery, there is increased inflammatory activity; C-reactive protein, fibrinogen, antithrombin and platelet counts increase during the first week postpartum [27]. Blood coagulation returns to normal in the first 6–8 weeks postpartum [30, 35].

2.2. Other risk factors for thromboembolism

Along with the haemostatic changes mentioned in Section 1.1, increased venous capacitance and compression of large veins, such as inferior vena cava and iliac vein, by the growing uterus cause stasis [51] and additionally increase the thrombotic risk.

In addition to pregnancy-specific factors, the thrombotic risk increases in the presence of other elements such as thrombophilia. Both acquired (antiphospholipid syndrome) and inherited (such as factor V Leiden, prothrombin gene mutation G20210A, protein S deficiency, protein C deficiency, antithrombin deficiency) thrombophilic conditions are among

the factors taken into consideration when calculating the individual thrombotic risk [52–54]. The grade to which these factors contribute varies depending on the specific thrombophilia. There is also evidence that women with thrombophilia have a greater risk of pregnancy complications such as placental abruption, pre-eclampsia, foetal growth restriction, stillbirth and possibly recurrent miscarriage [55].

Other factors that increase the risk for thrombosis, in both pregnant and non-pregnant population, are a medical history of previous VTE, positive familial history for VTE, immobilization, obesity, etc. [56]. Some of those factors are very important when stratifying the individual risk for VTE during pregnancy and deciding on appropriate treatment strategy.

3. Venous thromboembolism in pregnancy and postpartum

3.1. Incidence and type of venous thromboembolism

The risk for VTE during pregnancy is increased, with rates varying from 4 to 50 times higher than in the non-pregnant population. However, despite the increased risk for VTE during pregnancy, the incidence is rather low. In the United States, venous thrombosis occurs in about 1 in 500–2000 pregnancies [57, 58], with DVT being 3–4 times more usual than PE [19, 59]. In Europe the incidence is about 0.71 per 72,000 deliveries, with two-thirds occurring prenatally and the remaining one-third postnatally [60]. The risk for VTE is most pronounced during the postpartum period. Most studies show that the antenatal risk for DVT is equally distributed among the three trimesters [57, 58, 61], whereas PE occurs more often (up to 60%) 4–6 weeks postpartum [62]. During pregnancy, the thrombotic risk is additionally enhanced by the presence of factors such as multiple births, inflammation, infection and diabetes [63, 64]. On the other hand, during the postpartum period, the risk increases in the presence of factors such as caesarean section, obstetric bleeding, pre-eclampsia/eclampsia and infection [20, 64], indicating that the risk factors for thrombosis during puerperium are different compared to the risk factors during pregnancy.

Pelvic vein thrombosis is a rare event outside of pelvic surgery and pregnancy. However, its incidence increases from accounting for less than 1% for all DVT events to 10% of all DVT cases during pregnancy [65]. Additionally, pregnancy-associated pelvic thrombosis is believed to be isolated and not originating from a distal part of the leg [66]. The majority (ca. 90%) of DVT during pregnancy is located in the left leg, probably as a result of the compression of the left iliac artery by the right iliac artery and the inferior vena cava by the growing uterus [58, 67].

3.2. Anticoagulant treatment

Despite the differences in dose recommendations among different committees, the preferred drug for treating VTE during pregnancy is unanimously low molecular weight heparin (LMWH), replacing the previous recommendation on the use of unfractionated heparin (UFH) [68, 69]. LMWH has been shown to cause less bleeding episodes and has a lower risk of causing heparin-induced thrombocytopenia (HIT) and osteoporosis compared to UFH [70, 71]. In contrast to vitamin K antagonists that cross the placenta and can cause

teratogenicity, LMWH does not cross the placenta, is easy to administer and has a consistent bioavailability [72]. Fondaparinux does not cross the placenta either, but its use during pregnancy has not been studied extensively; it is primarily recommended for patients with allergy to heparin or HIT [62].

Considering the significant morbidity and mortality associated with VTE during pregnancy and postpartum, prompt diagnosis and treatment of thrombosis is essential to ensure a good maternal and foetal outcome. Although there have not been any major studies on the safety of treating pregnant patients with DVT as outpatients, data from the treatment of non-pregnant patients suggest that this is safe as long as the patient's condition allows it [62]. On the other hand, the safety of treating patients with PE at home, especially on the first days following the event, is more uncertain.

There is no international consensus on the optimal dose for treatment of VTE during pregnancy. LMWH is predominantly eliminated renally, and in the non-pregnant population with a glomerular filtration rate (GFR) of more than 30 mL/min, e.g. no severe renal function impairment, there is no need to adjust the dose or monitor the treatment. However, in pregnant women, due to increased plasma volume and subsequent heparin clearance, as well as weight increase [73], the need for both dose adjustment and monitoring can arise, though expert opinions dissent on that. The initial dose depends on the maternal weight according to the guidelines for non-pregnant patients [69]. The following dosages are recommended for the most commonly used LMWH: dalteparin 200 units/kg once daily or 100 units/kg every 12 hours, tinzaparin 175 units/kg once daily, enoxaparin 1 mg/kg every 12 hours and nadroparin 86 units/kg every 12 hours or 171 units/kg once daily [69]. In Sweden, the recommended start dose of LMWH (dalteparin) is 125 units/kg twice daily or 250 units/kg once daily, since pregnant women need more (25–30%) of LMWH compared to non-pregnant women [74]. The twice-daily protocol is usually preferred in Sweden since clinical observations have indicated a lower bleeding risk.

There is no consensus on whether LMWH should be given once or twice daily, either. Some physicians choose the twice-daily regimen in order to better accommodate the changes in the plasma volume and renal clearance of LMWH during late pregnancy. However, it has been shown [75, 76] that the risk of recurrence does not increase with once-daily anticoagulant regimens in pregnant patients. This, combined with the simplicity of the once-daily treatment and the need for good compliance, makes it an attractive alternative for many physicians and patients.

There are different approaches for the rest of the treatment, following the initial dose, mainly on whether the dosage should be adjusted. In some centres, the dose remains unchanged throughout pregnancy [77]. If an adjustment is deemed necessary, it can be performed either according to the patient's increasing weight [77, 78] or by periodically measuring anti-Xa LMWH levels [69, 73]. The target level is most commonly set to 0.6–1.0 units/mL for a bid regimen and higher for a once-daily regimen, measured 4–6 hours following administration [62]. There are, however, data suggesting that those adjustments are not necessary in most women receiving therapeutic dose of anticoagulants [79–81] showing neither an increase in safety and efficacy of treatment nor a decrease in bleeding complications. The tests currently utilized for the measurement of anti-Xa LMWH are costly and have been reported to be not

always reliable [69]. As such, there is no general recommendation on the use of such tests for dose adjustments, but such tests can be useful in patients with renal impairment and extreme low or high body weight [69].

A review by Gandara E et al. [82] on studies where women who were treated with full-dose anticoagulation for up to 6 weeks following diagnosis of VTE (predominantly DVT) and then changed to a dose somewhat lower than 75% of full dose but higher than prophylactic dose, showed that the risk for recurrence was low (ca. 0.65%). In the American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines from 2012, dose reduction is named as an alternative approach, especially in patients with high risk of complications, such as osteoporosis and bleeding [62].

Unfractionated heparin can be used as alternative to LMWH in some cases, for example, in patients with severe renal impairment as well as when thrombolysis is considered or when urgent surgery or delivery is planned. When UFH is given, the recommended regimen is twice daily, with doses adjusted to prolong activated partial thromboplastin time (aPTT) into therapeutic range as measured 6 hours following administration [69]. Caution is advised since it is known that aPTT measurement during pregnancy is not as reliable as in non-pregnant patients. The increased levels of factor VIII and of heparin-binding protein observed during pregnancy lead to corresponding decreases in aPPT and increased UFH requirement. It is unclear whether the attenuation in dosage leads to significant bleeding complications [77].

Data on thrombolysis during pregnancy, including data on maternal and foetal safety, is very limited. As such, thrombolytic treatment should be discussed only in the setting of life-threatening PE or in cases of severe DVT where there is a risk of losing a limb [62, 69].

Choosing a delivery option for women on anticoagulation should optimally have been discussed in advance by a multidisciplinary team of coagulation experts, obstetricians and anaesthesiologists. The decision should be based on factors such as the patient's risk profile for both bleeding and thrombosis, the time elapsed since diagnosis of VTE and the actual dosage of anticoagulants, as well as the patient's own preferences. Planned labour induction can be successful in preventing anticoagulation-associated bleedings during partus. In order to ensure patient safety, it is recommended to discontinue anticoagulant treatment 24 hours prior to delivery or neuraxial anaesthesia [62].

The optimal duration of anticoagulation is under discussion. Considering the fact that the increased risk for thrombosis persists throughout pregnancy and puerperium, the current recommendation is that anticoagulation continues for the duration of pregnancy for at least 6 weeks postpartum for a minimum time period of 3 months [62, 69].

3.3. Efficacy and safety of anticoagulant treatment: therapeutic dose

The major adverse effect of treatment with anticoagulants is bleeding. According to the ACCP guidelines from 2012 [62], major nonfatal maternal haemorrhage is defined as a symptomatic bleeding complication into a critical site (intracranial, intraspinal, retroperitoneal, pericardial, etc.), under pregnancy or within 6 weeks postpartum that results in a fall in haemoglobin level of 20 g/L and to transfusion of two or more units of whole blood or red cells [83].

According to a study from 1989, the risk for major antepartum bleeding in pregnant women under anticoagulation with UFH is about 1%, e.g. comparable to the rates noted for non-pregnant patients [72]. LMWH, the drug of choice for treatment and prevention of VTE during pregnancy, has an even milder bleeding complication profile compared to UFH [71, 84]. A review by Greer IA et al. [85] reported bleeding rates of 0.43% (for antepartum haemorrhage) and 0.94% for postpartum haemorrhage (PPH). PPH is defined as blood loss exceeding 500 ml (vaginal delivery) or 1000 ml (caesarean delivery) and is divided into primary PPH, occurring within the first 24 hours after partus, and secondary, occurring between 24 hours up to 12 weeks after partus [86]. Primary PPH has been reported to occur in 1.9% of women receiving treatment dose of anticoagulants [84]. In a study by the authors (unpublished data) on 39 patients with antenatal pelvic vein thrombosis treated with full (adjusted)-dose LMWH, the risk for PPH (<1000 ml) was somewhat increased; however, the risk for severe PPH (>1000 ml) was not increased compared to women without anticoagulation therapy [87], and the rates were comparable to other studies [86]. In the majority of those patients, LMWH was discontinued 24 hours prior to delivery. Knol et al. [86] did not observe an increase in the number of transfused red blood cell units in a population receiving full-dose anticoagulation, suggesting that the majority of observed PPH lacked major clinical significance and the treatment should be deemed safe.

The risk for both HIT and osteoporosis is lower with LMWH compared to UFH [88, 89]. Long-term treatment with UFH has been reported to cause osteoporotic fractures in 2–3% of patients [90], with the rate increasing to 15% in older populations for UFH but being lower for LMWH (3%) [91]. The risk for HIT in patients with UFH has been reported to vary from 0.8% [92] to 2.7% [70] with the respective rates for patients with LMWH being 0% (70). However, antibodies developed in patients with HIT under treatment with UFH have a high risk of cross-reacting with LMWH if such treatment is given [93].

No recurrent thrombosis was recorded for the remainder of their pregnancies in women with pelvic vein thrombosis in the study by the authors mentioned earlier (unpublished data). Similarly, in other studies, the recurrence rates for patients receiving anticoagulant treatment were low [75], indicating a high efficacy of treatment.

4. Thromboprophylaxis in pregnancy and postpartum

The cornerstone of the pharmacological treatment for prevention of recurrent or first-time VTE is LMWH [69]. The grade of the recurrence risk depends on the risk factors for thrombosis, such as previous VTE, thrombophilia and family history, and the patients are treated accordingly.

4.1. Risk stratification for recurrent venous thromboembolism during pregnancy and postpartum

A history of previous thrombosis is the strongest risk factor to predict recurrence risk [94]. Among studies of different designs, the risk for recurrent VTE in women not receiving thromboprophylaxis ranges from 2.4% [95] to 6% [96]. Despite the relatively low recurrence rate,

the potentially catastrophic implications of an antenatal or postpartum VTE for mother and foetus have to be considered.

In order to evaluate the risk for thrombotic recurrence and decide on the type of recommended prophylaxis, the patients can be divided into four groups of increasing risk according to the following suggestion: (a) low risk (previous VTE provoked by a transient risk factor), (b) intermediate risk (spontaneous VTE or VTE associated with hormonal treatment or pregnancy), (c) high risk (multiple previous VTE or permanent risk factors for thrombosis) and (d) very high risk (patients with previous VTE and indication for continuing treatment with anticoagulants) [62, 69]. Postpartum (6 weeks following delivery) thromboprophylaxis with LMWH or vitamin K antagonists should be considered for all groups, and the need for additional antenatal prophylaxis should be carefully assessed for groups b–d [62, 69]. These recommendations are subject to change, and the patient can be recommended ante- and/or postpartum prophylaxis depending on the concomitant presence of additional risk factors [68, 69, 97]. If antenatal prophylaxis is given, it should be introduced early upon confirmation of pregnancy [69].

4.1.1. Risk stratification for first-time venous thromboembolism during pregnancy according to family history and thrombophilia

The risk for VTE in individuals with thrombophilia varies, with the highest risk observed on patients with homozygosity for factor V Leiden and prothrombin gene G20210A mutation, whereas the corresponding heterozygotes had considerably lower risks [98]. Familial history of VTE further increases the risk for a first-time thrombosis during pregnancy by two- to fourfold [99].

Similarly to Section 3.1.1, women with thrombophilia and heredity for VTE without previous VTE are divided into different risk groups: (a) women with family history who are homozygous for factor V Leiden or prothrombin gene G20210A mutation, (b) women with family history and all other thrombophilias, (c) women without family history who are homozygous for factor V Leiden or prothrombin gene G20210A mutation and (d) women with all thrombophilias except for those mentioned in (a) without family history. Antenatal and postpartum prophylaxis is recommended for group a, whereas groups b and c are thought to benefit from 6 weeks postpartum thromboprophylaxis. No drug treatment is required for women in group d, unless in the presence of other risk factors, most significantly caesarean section [62, 69]. A special mention should be made to antithrombin deficiency, which is the only other thrombophilia, except for those mentioned in (a) that could warranty antepartum prophylaxis [69].

4.1.2. Risk stratification for first-time venous thromboembolism during pregnancy according to clinical factors

Factors such as BMI > 25 (prior to pregnancy), immobility, caesarean section and co-morbidities (e.g. systemic lupus erythematosus, sickle cell disease) increase the risk for thrombosis independently of the presence of thrombophilia and family history [64, 100]. The extent to

which the thrombotic risk is increased by those factors individually is unclear, but is generally considered as modest [62]. However, when antepartum immobility is combined with co-morbidities, the clinician should consider administering thromboprophylaxis during pregnancy and shortly postpartum (7 days) [69].

4.2. Type of thromboprophylaxis

The optimal dose of LMWH thromboprophylaxis is unclear, since studies that compare the different dosages are lacking. For patients with previous VTE who have intermediate or high risk for recurrent thrombosis during pregnancy (see 3.1), it is recommended to use prophylactic or intermediate-dose LMWH. Examples of prophylactic dose LMWH are dalteparin 5000 units subcutaneously every 24 hours, tinzaparin 4500 units subcutaneously every 24 hours, nadroparin 2850 units subcutaneously every 24 hours or enoxaparin 40 mg subcutaneously every 24 hours [62, 96, 101]. Examples of intermediate-dose LMWH include dalteparin 5000 units subcutaneously every 12 hours or enoxaparin 40 mg subcutaneously every 12 hours [62]. The aforementioned dosages can be adjusted depending on body weight and/or renal function [62].

The recommended dose for patients at very high risk for recurrent VTE is higher (adjusted dose or 75% of therapeutic dose) [69]. Adjusted LMWH dose is the dose required in order to maintain a peak level of anti-factor Xa LMWH of 0.2–0.6 units/mL [102] or a trough level of 0.1–0.2 U/ml [103]. For women without a history of VTE who require thromboprophylaxis, it is recommended to administer prophylactic or intermediate-dose LMWH [62]. However, the decision on the optimal dosage is individual, and factors such as risk for complications (bleeding) and patient preferences should be weighed in.

4.3. Efficacy and safety of anticoagulant treatment: prophylactic dose

The risk of bleeding with prophylactic dose of LMWH is generally low and the treatment is considered safe. Most studies in the field do not make a distinction between high- and normal-dose thromboprophylaxis, which makes the results difficult to interpret and the bleeding rates cannot be surely attributed to one type of treatment. In a recent study the bleeding rates were very low according to data derived from 10 studies where the patients were given normal-dose thromboprophylaxis, with overall antepartum rates for severe bleeding (ISTH definition [83]) reported as low as 0% and postpartum rates as 0.3% [104]. In a study by Lepercq et al. that was not included in the meta-analysis in [94], a bleeding incidence of 11.5% was reported; however, in this study, patients with both high and normal prophylaxis doses were included [105]. In a study by the authors, the incidence of bleeding during pregnancy was 12% (n = 6) and postpartum haemorrhage had an overall incidence of 20% (n = 10) in a cohort of 49 patients treated with high-dose thromboprophylaxis at the Department of Obstetrics and Gynaecology at Karolinska University Hospital in Solna for a time period from 2004 to 2014 (unpublished data). In the same cohort, the incidence of VTE was 2% (n = 1, unpublished data). In a study by Pettilä et al. where the patients were treated with normal-dose thromboprophylaxis (UFH or dalteparin), the VTE incidence was 0% [106].

The mean bone density of patients treated with prophylactic doses of LMWH (dalteparin) did not differ from that of patients treated with placebo whereas for patients treated with UFH it was significantly decreased [107]. Similarly, in another study, no difference in bone density was observed between patients receiving prophylactic doses of LMWH and placebo [88]. There are, however, some case reports confirming LMWH-associated osteoporosis [62], and the risk for each patient should be evaluated individually.

5. Future perspectives

5.1. Direct oral anticoagulants

Pregnant and lactating women were excluded from the clinical trials on direct oral anticoagulants (DOAC), e.g. dabigatran, rivaroxaban, apixaban and edoxaban, as there is data suggesting that they may cross the placenta with unclear effects [108]. A recent article [109] identified 233 cases where pregnant women had been exposed to DOAC, with the majority having been exposed to rivaroxaban. The authors did not report an increased risk for embryotoxicity; however, the number of patients was small and the reports were incomplete and diverse [109]. There are currently no guidelines recommending the use of DOAC during pregnancy and breast-feeding.

5.2. Studies

Despite the effectiveness and safety of anticoagulant treatment during pregnancy and postpartum, issues such as the optimal way to adjust and monitor the therapeutic dose of LMWH but also the ideal dose and duration of thromboprophylaxis are yet to be conclusively addressed. Additionally, although there are guidelines from different work groups, differences in local practice remain. There is a need for studies on larger cohorts under international collaborations in order to further advance treatment efficacy and ensure patient safety.

Author details

Roza Chaireti[1,2]* and Katarina Bremme[3]

*Address all correspondence to: roza.chaireti@ki.se

1 Department of Haematology, Karolinska University Hospital, Solna, Sweden

2 Department of Molecular Medicine and Surgery, Karolinska Institute, Solna, Sweden

3 Department of Women's and Child's Health, Karolinska Institute, Solna, Sweden

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