REVIEW ARTICLE

Venous thromboembolism and pregnancy: A review of the literature

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Abstract

This review aims to provide the mother carers with the most recent evidence-based guidelines in the context of managing of pregnancy-associated VTE, where an extensive search through the medical journals addressing the topic including the medical database such as Pubmed, Medline, Sience direct,Embase and others using the title and key-words in order to gather the most concerned as well as the up-to-date publications concerned with the problem under research, the search resulted in recognising pregnancy as a significant risk factor for the development of VTE, both during the prenatal and postnatal periods, with an estimated increased likelihood risk of five and sixty times, respectively and concluded that venous thromboembolism (VTE) is one of the leading causes of maternal mortality hence, all pregnant women should be assessed for the risk of developing the condition as early as possible (when scheduling a booking antenatal appointment) or even in the pre-pregnancy clinic. *(Afr J Reprod Health 2023; 27 [5]: 81-94).*

Keywords: Thromboembolism, maternal mortality, heparins, pregnancy, thrombocytopenia

Résumé

Cette revue vise à fournir aux mères soignantes les directives les plus récentes fondées sur des preuves dans le contexte de la prise en charge de la TEV associée à la grossesse, où une recherche approfondie dans les revues médicales traitant du sujet, y compris la base de données médicale telle que Pubmed, Medline, Sience direct ,Embase et d'autres utilisant le titre et les mots-clés afin de rassembler les publications les plus concernées ainsi que les publications les plus récentes concernant le problème à l'étude, la recherche a abouti à reconnaître la grossesse comme un facteur de risque important pour le développement de TEV, à la fois pendant les périodes prénatale et postnatale, avec un risque de probabilité accru estimé de cinq et soixante fois, respectivement, et a conclu que la thromboembolie veineuse (TEV) est l'une des principales causes de mortalité maternelle, par conséquent, toutes les femmes enceintes devraient être évaluées pour le risque de développer la maladie le plus tôt possible (lors de la prise d'un rendez-vous prénatal) ou même dans la clinique de pré-grossesse. *(Afr J Reprod Health 2023; 27 [5]: 81-94).*

Mots-clés: Thromboembolie, mortalité maternelle, héparines, grossesse, thrombocytopénie

Introduction

Pregnancy is recognised as a significant risk factor for the development of VTE, both during the prenatal and postnatal periods, with an estimated increased likelihood risk of five and sixty times, respectively[1]. Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) are the two most frequent sites where venous thromboembolism can occur[2,3]. Although it is a rare location for VTE, Cerebral Venous Thrombosis (CVT) is a significant

cause of stroke in young people[4]. The rate of objectively-confirmed cases of DVT and PE varies between 0.6 and 1.3 cases per 1000 births, which is 5–10 times greater than the incidence seen in non-pregnant women[5]. Pregnancy-related haemostatic alterations, in which the concentration of the clotting factors fibrinogen, II, VIII, Von Willbrand factor, IX, X, and XII is increased, are principally responsible for this considerable rise in thrombotic tendency. Additionally, the growing gravid uterus' mechanical obstruction of the venous outflow, when combined with either hereditary or acquired forms of thrombophilia, creates a cumulative risk for thromboembolism during pregnancy and the postpartum period.Of note, PE is suggested to be the primary factor (20%) in maternal mortality, surpassing other pregnancy-related complications like bleeding, sepsis, and pregnancy-induced hypertension[6].

Individual risk factors for pregnancy-related VT

Prior VTE is the most significant risk factor for VTE during pregnancy, and women with a personal history of DVT and/or PE have a three- to four-fold higher risk of VTE recurrence during pregnancy than they do outside of pregnancy[5]. The absolute risk of recurrent VTE during pregnancy without the use of pharmacological prophylaxis was shown to be 2.5% in a large prospective research that studied 125 pregnant women with a single prior episode of VTE[6]. The absolute incidence of VTE recurrence in the antepartum period for women with prior VTE who did not receive pharmacological prophylaxis ranged between 5.8 and 10.9 % in two further retrospective trials[5,7]. However, the extent of the recurrence risk will depend on the circumstances surrounding the initial VTE; this risk will be higher if the initial VTE episode was connected to a high oestrogen state (e.g., provoked by oral contraceptive use, connected to pregnancy, connected to the postpartum period), as opposed to if the primary VTE episode was unrelated to or connected to a non-hormonal transient risk situation (e.g. trauma, surgery or immobility)[5,7,8]. Hereditary thrombophilia and positive family history of VTE are also known risk factors for the development of VTE during pregnancy and the postpartum period. At least one heritable thrombophilia is found in 20 to 50 % of pregnancy-related VTE[9,10]. with proven increased risk in women with inherited multiple thrombophilic defects[10]. The prothrombin G20210A mutation (PGM) and factor V Leiden (FVL), which are present in about 5 and 2% of the healthy population, respectively, are the two inherited thrombophilias that predispose to VTE most frequently in the European population[11].

However, women who are heterozygous for FVL or PGM and do not have any additional risk factors are considered to have a low risk of VTE in the antenatal and postpartum periods (absolute risk around 1%)[9,12]. In contrast, pregnant women who are homozygous or combined heterozygous for FVL and PGM are at an especially higher risk of VTE, with an increase of the absolute risk of up to 4 to 14 %[13]. The risk of VTE, on the other hand, appears to be as low as 1 % in the antepartum and postpartum periods in pregnant women with Protein C(PC) or Protein S(PS) deficiencies who have no prior or familial history of VTE[14]. In conclusion, we define severe deficiencies of the natural coagulation inhibitors AT, PC, and PS as well as homozygosity for FVL and PGM as high risk thrombophilias, whereas heterozygosity for FVL or PGM is considered as low risk thrombophilias, all of which are taken into consideration when assessing the risk of VTE. Additionally, a positive family history of VTE, particularly in first-degree relatives, increases the individual thrombotic risk in a pregnant woman with hereditary thrombophilia by two to four times[15].

Antiphospholipid syndrome (APS) is the most prevalent acquired thrombophilic disease in pregnant women[16]. Antiphospholipid (APL) antibodies, such as β -2-glycoprotein (b2GP1) are characteristically present in APS with recurrent vascular thrombosis (both arterial and venous) and poor pregnancy outcomes, including recurrent miscarriage, preterm birth, placental abruption, and foetal growth restriction, are the main presentations of pregnancy-associated APS[17]. Notably, the number of positive APL tests and the quantity of antibody titres both increase the risk of developing thrombosis and subsequent pregnancy morbidity. This risk is especially high in pregnant women who have triple APL positivity (i.e., lupus anticoagulant, anti-cardiolipin immunoglobulin G[IgG] or IgM, and anti-b2GPI IgG or IgM positivity)[18].

When compared to vaginal delivery, Caesarean section delivery carries a two to four fold greater risk of VTE (OR=2)[3,19,20], with a pooled incidence rate of 2.6 per 1,000 Caesarean deliveries and a significantly higher incidence with emergency Caesarean sections[16] . However, in healthy women having an elective Caesarean delivery, the risk of VTE is low[17].

Obesity is a recognised risk factor for VTE in pregnancy[3,16,21,22]. In a population-based nested case-control research, Larsen *et al.* found that the adjusted OR for obesity with a body mass index (BMI) >30 kg/m2 was 9.7 (95% CI: 3.1-30.8) during pregnancy and 2.8 (95% CI: 0.8-9.8) in the postpartum period[21].

Multiparity (>3 children),in a large cross-sectional study by Al-zakwai *et al.* (2016), was discovered to be the second most common risk factor, seen in 33% of patients, after obesity, which manifested in 76% of the examined VTE[23].

Antepartum immobilization,which is defined as strict bed rest for 7 days or more during pregnancy, has been identified as a strong risk factor for VTE during pregnancy and post partum period and a multiplicative effect of immobilization and obesity on VTE risk has been observed in women with an increased BMI[24].Further, it has been demonstrated that the risk of VTE in pregnant women is raised during hospitalizations unrelated to birth (relative risk: 17.5; 95 % CI: 7.7-40.0) and continues to be significantly high for 28 days after discharge[25].

In comparison to the general pregnant population, the risk of VTE after assisted reproductive technologies (ARTs) is increased by around a factor of two[25]. The risk per cycle of in vitro fertilisation (IVF), however, is still considered to be very low at 0.1 to 0.3%[26,27]. Women with ovarian hyperstimulation syndrome (OHSS), in whom the absolute risk of VTE rises to 1 to 4 % in cases of severe OHSS, account for the majority of thromboembolic events following ARTs. It should be noted that OHSS patients are especially vulnerable to jugular and upper extremity DVT[28,29]. Multiple pregnancies, advanced maternal age (over 35), medical comorbidities (such as diabetes mellitus and hypertension), dehydration, malignancy, and surgical operations during pregnancy are additional, but less common, risk factors for pregnancy-related VTE[30] .

Risk assessment of pregnancy-related VTE

Due to the fact that VTE is one of the main causes of maternal mortality, all pregnant women should be assessed for the risk of developing the condition as early as possible (when scheduling a booking antenatal appointment) or even in the pre-pregnancy clinic with Special consideration should be given to women who have experienced previous VTE, are known to be thrombophilic, and/or have a family history of the condition[31].

The risk scoring approach should be used to assess the need for thromboprophylaxis during pregnancy and the postpartum period. The pregnant women will then be classified into different risk levels based on the associated risk factors, and the appropriate thromboprophylaxis regimen is then prescribed. This regimen may include observation alone, mechanical methods, or low molecular weight heparin (LMWH)[32], the choice of which should be individualized according to patient's associated risk factors[14].

However, with the exception of women who have had a prior VTE, for whom there are reasonably unambiguous recommendations for medicinal thromboprophylaxis from current guidelines [33–37],there are multiple risk stratification suggestions in current guidelines, which will result in varied thromboprophylaxis recommendations.

If pharmacological thromboprophylaxis is considered during pregnancy or the puerperium, the risk of VTE must be significantly higher than the risk of serious bleeding complications due to anticoagulant medication. These factors have been taken into account by certain guidelines and expert panels, leading to suggestions that the absolute risk of VTE must be more than 1 to 5% before the woman will benefit from pharmacologic prophylaxis[37,38] ,with the woman's values and prefrences should be prioritized and given the lack of data from appropriate studies and weakness of many recommendations[39].

General recommendations for prevention of pregnancy-related VTE

The use of thromboprophylaxis during pregnancy and puerperium is generally endorsed by current international guidelines, which include[14].

1. Prior to conception, during pregnancy, before and after delivery, if being hospitalised for a reason other than delivery, women should have a personalised VTE risk assessment performed.
2. During the booking antenatal appointment, women who are at high risk for VTE should receive counselling regarding the symptoms and warning signs of VTE as well as instructions to report immediately to the nearest medical facility in the event of an emergency.
3.The decision to administer thromboprophylaxis should be based on the absolute risk of VTE during pregnancy and puerperium, and it must also take into account the patient's preferences and the absolute bleeding risk of the anticoagulant.

Specific recommendations for prevention of pregnancy-related VTE

Women with heterozygous FVL or heterozygous PGM without prior VTE and with or without family history of VTE(VTE absolute risk <3% and <1%,respectively),are not recommended for pharmacological thromboprophylaxis by most of the current guidlelines[33–35,37,41]. with a follow-up strategy to evaluate the symptoms and warning signs of DVT and PE and advise the patient on when to seek medical advice, as well as future evaluation[42] . Others, advise a brief course of LMWH for 2 weeks postpartum for women who have no family history of VTE and have additional risk factors (such as hospitalization)[43] or for patients who have a strong prefrence for the treatment, despite the fact that the benefits are questionable[40].

Women who have homozygous or compound heterozygous variants of FVL or PGM are far more likely to experience venous thromboembolism during pregnancy (absolute risk around 4-14%) Thus, pharmacological thromboprophylaxix for 6 weeks following delivery has been advised[44–47], and additional antepartum thromboprophylaxis covering the entirety of the pregnancy is encouraged by several guidelines, especially in cases linked to a positive family history or additional VTE risk factor[32-36,40]. Contrarily, the American College of Chest Physicians (ACCP) recommends only clinical vigilance (i.e., the pregnant woman and her physcians are aware of potential risk factors and situations as well as the symptoms and signs of VTE) as the management strategy of choice and only recommends pharmacological thromboprophylaxis for those women with a positive family history or exhibit additional risk factors[33].

Women with hereditary deficiencies of Protein C, Protein S, or Antithrombin without prior VTE and without a family history of VTE tend to have a low VTE risk (1%) hence, thromboprophylaxis during pregnancy is not typically advised in current guidelines[14]. The most recent ACCP and ASH guidelines only advise antepartum and postpartum clinical vigilance rather than pharmacological thromboprophylaxis for women with PC and PS deficiencies who have not previously experienced VTE or have a family history of VTE (as considered to have a minor risk factor)[33,35]. However, the majority of the current guidelines continuously advocate pharmaceutical thromboprophylaxis for 6 weeks post partum due to the substantially increased risk of VTE in women with additional positive family history of VTE[33-36,39]. Notably, because patients with AT deficiency are thought to be at an increased risk of VTE (the reported risk is 3% to 8.3 % in the combined antepartum and postpartum periods)[48,49] compared to those with PC and PS deficiencies(1%), some guidelines recommend antepartum and postpartum thromboprophylaxis for AT deficiency women[33,35,37] with monitoring of anti factor-Xa level and LMWH dose adjustment may be required[50,51].

For women with APS and prior obstetric complications (such as recurrent miscarriage, preterm birth, placental abruption, and foetal growth restriction), Lesile Sheith (2017)[40] does not routinely recommend antepartum LMWH for VTE prevention during pregnancy unless there were additional risk factors present or there was a prior history of VTE. However, he advises postpartum LMWH prophylaxis in patients who have lupus anticoagulant (LAC), higher titer anti cardiolipin (aCL)IgG or IgM antibodies/LAC, or if there are other risk factors present, such as systemic lupus erythematosus (OR 8.7)[41].

Women with prior VTE, whether unprovoked or estrogen- related VTE, are more likely to have recurrence of thrombosis during pregnancy[5–7]. Therefore, they should be offered pre

pregnancy councelling and a prospective management plan of antepartum thromboprophylaxis with LMWH covering the entire pregnancy and for 6 weeks postpartum[36,42]. If the patient was not already on anti-coagulant therapy, The LMWH should be started as soon as the pregnancy is confirmed[14]. However, for pregnant women with a prior provoked VTE originating from a major risk factor such trauma, surgery, or protracted immobilisation. Lesile Skeith[42] exclusively suggests postpartum thromboprophylaxis because the likelihood of antepartum VTE recurrence appears lower (1%)[46]. Whereas he used to make an individualised decision based on the type of provoked event, thrombophilia, and patient values and preferences[40] because there is minimal information indicating whether thrombophilia increases the incidence of VTE[5-7]. In addition, little is known regarding the likelihood of cerebral vein thrombosis recurrence in pregnancy[46]. However, it may be helpful to perform a baseline compression ultrasound on the previously affected limb before or during pregnancy to assess the amount of remaining thrombus material and any post-thrombosis alterations[33]. It is important to note that women with prior VTE who are taking long-term anticoagulation therapy, such as direct oral anticoagulants (DOAs) or vitamin K antagonists (VKAs), should receive pre-pregnancy counselling and be made aware of the risks of taking oral anticoagulants while pregnant, specifically foetal teratogenicity (because these medications cross the placenta) and bleeding complications. They should then be given the option to switch to LMWH either before pregnancy or right away once having a positive pregnancy test performed on delayed or missing period occurs[14,52–55].

For women with VTE risk factors other than thrombophilias and due to the lack of evidence regarding the benefits of anti-thrombotic therapy during pregnancy, the use of pharmacological thromboprophylaxis for isolated pregnancy-related risk factors (which typically do not increase the absolute risk of VTE greater than 1%[12,24]), cannot be advised[14]. However, temporary thromboprophylaxis should also be taken into account in patients with hyperemesis gravidarum, especially if associated with hospitalisation, and in women undergoing non-obstetrical surgery during pregnancy, as well as in women with a BMI ≥30 kg/m2 or with multiple risk factors and prolonged immobilisation (i.e.≥ 7 days)[26,34]. Whereas, for ART-induced pregnancies, routine thromboprophylaxis is not advised unless there are other risk factors. It should be noted that in cases of severe OHSS, LMWH prophylaxis for up to 3 months after the condition has resolved should be considered[14].

Preventive strategies for pregnancy-related VTE

Mechanical thromboprophylaxis, which involves the use of Intermittent Pneumatic Compression (IPC), Anti Embolism Stockings (AES), and Graduated Compression Stockings (GCS) for the prevention of VTE during pregnancy and puerperium, has not been proven effective in clinical trials and is therefore generally viewed as inferior to pharmacological thromboprophylaxis with proved higher efficacy in preventing the pregnancy-associated VTE (RR 0.58; 95%CI:0.35-0.96)[56]. In light of this, mechanical prophylaxis may be thought of as a supplement to pharmaceutical thromboprophylaxis. However, patients for whom the use of anticoagulants is contraindicated, such as those who are actively bleeding or are at high risk of bleeding but have a clear need for antithrombotic therapy, may benefit from the use of AES and ICP. Additionally, GCS is advised for expectant mothers who have symptoms of chronic venous insufficiency brought on by varicosities or post-thrombotic syndrome[14].

Parenteral antithrombotic medications, such as heparins (Low molecular weight heparins and Un fractionated heparin) and heparin-like anticoagulants (Fondaparinux and Danaparoid), do not cross the placental barrier and are not significantly excreted in breast milk. Additionally, there is no evidence that their use increases the risk of foetal bleeding or teratogenicity[33]. Heparins are therefore regarded as the antithrombotic agent of choice for the prevention and treatment of VTE during pregnancy and the puerperium.

Fondaparinux and danaparoid are alternative options in the event that a patient has a contraindication to heparins due to, for example, side effects[33,34,36,45,50]. Low molecular weight heparins (LMWH), administered subcutaneously, are often favoured over unfractionated heparins

(UH), as they are linked to a substationally lower incidence of side effects like heparin induced-thrombocytopenia(HIT),heparin-induced skin rashes, haemorrhage, and osteoporosis, compared to UH[57–62] . There are many dosages of LMWH that can be used during pregnancy (i.e. prophylactic,intermediate or therapeutic). However, there is still a lack of sufficient data from randomised controlled trials regarding the ideal dose regimens[34,63] , and the dosage decision is determined on an individual basis after careful evaluation of the woman's risk of VTE as well as the risk of bleeding[14]. Hart *et al.* (2020) summarizes the dose regimens of LMWH and alternative anti thrombotic agents (Table 1).

Patients who need VTE prevention during pregnancy or the puerperium and who are not on anticoagulant medication should generally get prophylactic doses of LMWH[14]. Lesile Skeith (2017) proposed a dosage regimen of a prophylactic dose of LMWH once per day until 20 weeks gestations (e.g., dateparin 5000IU once per day, enoxaparin 40 mg, or tinzaparin 4500 IU once per day), with an increase to a twice-daily dose once the pregnancy reaches 20 weeks till delivery due to early trough levels of anti-factor Xa activity caused by alterations in the volume of distribution and higher renal clearance during pregnancy[64,65], due to the fact that this regimen does not alter bone marrow density, no calcium or vitamin D supplement is necessary[66]. While an intermediate dose of LMWH should be considered in patients with significantly increased risk of VTE (e.g., prior VTE and moderate to severe AT deficiency), women on anticoagulation therapy before pregnancy are generally treated with intermediate or therapeutic doses of LMWH during pregnancy[14]. It should be emphasised that standard laboratory tests before to prescription LMWH should be done and should measure blood cell count, serum creatinine level, prothrombin time, and partial thromboplastin time (aPTT). Monitoring of platelet count is not recommended, though, because HIT risk in pregnant women on LMWH treatment is extremely low[67] . Once more, current recommendations do not support routine anti-Xa monitoring for prophylactic or therapeutic anticoagulation medication during pregnancy[33,34,36,50]. Measurement of anti-Xa peak levels, however, may be taken into consideration for therapeutic treatment in women who are at the extremes of body weight (i.e., 50 or >100kg) or in women who have additional complicating factors such severe renal impairment or severe thrombophilia[68].

Unfractionated heparin (UFH) may be used as an alternative to LMHH in women who have severe renal impairment (because LMWH is exclusively metabolized by kidneys), are at high risk for bleeding problems, are peripartum when considering regional anaesthesia. Fixed dosages of subcutaneous UFH are administered twice or three times daily for prophylactic purposes, whereas therapeutic doses often necessitate a continuous infusion and aPTT monitoring to obtain an anti-Xa level of 0.3 to 0.7 U/ml or a 1.5-2.5 fold prolongation of the aPTT[33,62]. To monitor UFH throughout pregnancy, anti-Xa activity is always preferred with a target anti-Xa level of 0.35 to 0.7 U/ml[14]. It should be noted that the aPTT response to UFH is frequently attenuated during pregnancy, making it unreliable for UFH monitoring during pregnancy[69].

Heparin-like anticoagulants, such as fondaparinux and danaparoid, due to the limited information on the foetal safety ,their routine usage during pregnancy is not advised[70–72]. However, their usage may be restricted to pregnant women with definitive heparin contraindications, such as HIT, severe allergic reactions, active bleeding or higher risk of bleeding (e.g. placenta preaevia),bleeding diathesis or acquired coagulopathy, thrombocytoprnia (platelets<$75x10^9$) acute stroke in the last 4 weeks, severe liver disease or uncontrolled hypertension[33,35,36,45]. Notably, the substantially longer half-lives of fondaparinux (15–20 hours) and danaparoid (22–24 hours) work against their use, particularly during the peripartum period[14].

Peripartum antithrombotic therapy

Pregnant women treated with antithrombotic therapy should have a timed councelling (e.g. between 32 and 36 weeks of gestation) regarding

Table 1: Dose regimens (daily dose) for pharmacologic anticoagulation during pregnancy (Adapted from Hart *et al.*[14])

Antithrombotic agent	Prophylactic dose	Intermediate dose	Therapeutic dose (weight-adjusted)
Low-molecular-weight heparin			
Dalteparin	1 × 5.000 IE	1 × 100–150 IE/kg 2 × 50–75 IE/kg	1 × 200 IE/kg 2 × 100 IE/kg
Enoxaparin	1 × 4.000 IE	1 × 100 IE/kg or 2 × 50 IE/kg	2 × 100 IE/kg 1 × 150 IE/kg
Nadroparin	1 × 2.850 IE	–	2 × 85 IE/kg or 1 × 171 IE/kg
Tinzaparin	1 × 4.500 IE	–	1 × 175 IE/kg
Alternative anticoagulants			
Fondaparinux	1 × 2.5 mg	–	1 × 7.5 mg ≤50 kg: 1 × 5 mg ≥100 kg: 1 × 10 mg
Danaparoid	2 × 750 IE	–	3 × 750–1,250 IE
Unfractionated heparin			
UFH	2–3 × 5.000 IE or 2 × 7.500 IE	–	80 IE bolus i.v., followed by 18 IE/kg/h i.v. or 2 × 150–250 IE/d s.c. target aPTT: 1.5 to 2 × baseline

Abbreviations: aPTT, activated partial thromboplastin time;IE, internationale Einheit (international unit); i.v., intravenous; s.c., subcutaneous; UFH, unfractionated heparin.

Table 2: Neuraxial anaesthesia in anti-coagulated patients: minimum time intervals without anticoagulation before and after catheter placement and removal (Adapted from Hart *et al.*[14]).

Antithrombotic medication	Half-life (h)	Before puncture/before catheter removal (h)	After puncture/after catheter removal (h)
Prophylactic dose regimen			
UFH, 2–3 × 5.000 or 2 × 7.500 IE/d	1.5–2	4	1
LMWH, prophylactic dose	4–6	12	4
Fondaparinux, 1 × 2.5 mg/d	15–20	36–42	6–12
Danaparoid, 2 × 750 IE/d	22–24	48	3–4
Therapeutic dose regimen			
LMWH, therapeutic dose	4–6	24	4
UFH, therapeutic dose	2–3	i.v. → 4–6 s.c. → 8–12	1
Fondaparinux, therapeutic dose	15–20	Neuraxial anaesthesia should be avoided due to a long half-life and potential accumulation	
Danaparoid, therapeutic dose	24		

Abbreviations: IE, internationale Einheit (international unit); i.v., intravenous; s.c., subcutaneous;LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

delivery-related issues and options available for intrapartum pain relief including neuraxial anaesthesia[14] . In general, vaginal delivery is the preferred mode of delivery for women who receive antithrombotic therapy for either prevention or treatment of pregnancy-associated VTE, and caesarean section is only preserved for otherwise obstetric indications due to the higher risks of bleeding complications as well as the thrombotic disease associated with caesarean section compared to vaginal delivery[73] . In either scenario, the thromboprophylactic-dose LMWH should be discontinued at the first sign of true labour pains, when labour is being induced, or at least 12 hours before the scheduled caesarean section[33,34,36]. However, if a woman is taking an intermediate or

therapeutic dose of LMWH, the medication should be stopped at least 24 hours prior to the scheduled delivery. If the risk of thrombosis was higher, such as in the case of a prolonged labour, additional doses of heparin, preferably of UFH due to its shorter half-life, have been recommended[34]. LMWH therapy at a prophylactic dose can then, be continued following vaginal delivery and in the absence of bleeding complications after a minimum of 4-6 hours, however it should be reintroduced in no less than 6-12 hours after vaginal delivery for patients on intermediate or therapeutic doses[74] . In low risk patients, thromboprophylaxis is not routinely advised after a caesarean section[75–77] unless complicated by additional risk factors, such as major postpartum haemorrhage or postpartum infection[78,79]. In these cases, prophylactic LMWH should be started or resumed 6-12 hours after the caesarean section and continued for at least 7 days up to 6 weeks postpartum. Nevertheless, if an intermediate or therapeutic dose is being considered, it should not be begun earlier than 12 to 24 hours following a caesarean section, assuming there were no bleeding complications[68]. Postpartum thromboprophylaxis with LMWH for at least 7 days should be considered for women having emergency caesarean sections[17,33,34.]

Peripartum neuraxial anaesthesia

During the prenatal period (often between 32 and 36 weeks of pregnancy), the woman should be informed about the effects of anticoagulant therapy on the use of peripartum regional analgesia/anesthesia and the alternatives to this intervention[14].The risk of delivery-related bleeding is estimated to range from 1:100,000 to 1:186,000, with an established increased risk associated with the use of heparins, low-dose aspirin, thrombocytopenia, or the presence of undiagnosed bleeding disorders. The incidence of bleeding complications, such as spinal/epidural haematoma after neuraxial anaesthesia in patients on heparin therapy, is unknown in terms of magnitude[79]. While neuraxial anaesthesia is still an option for patients receiving prophylactic doses of LMWH, it is not appropriate for individuals receiving intermediate or therapeutic dosages of the drug because the drug must be stopped at least 24 hours before to catheter insertion[80]. However, in patients receiving UFH, neuraxial anaesthesia may be considered as the drug can only be stopped for 4-6 hours if it was given intravenously and for at least 8-12 hours if it was given subcutaneously[14]. The suggested time intervals for catheter insertion or removal in patients who are anticoagulated are summarised in (Table 2)[14,80].

Postpartum antithrombotic therapy

Treatments with heparins, warfarins, and acenocoumarol while the newborn is nursing are regarded as safe[33].If the woman was previously taking LMWH at a prophylactic dose throughout pregnancy and it is planned to extend the thromboprophylaxis for varying lengths of time during the postpartum period, anticoagulant medication can be continued using LMWH. But if intermediate or therapeutic doses or longer periods of antithrombotic medication are necessary, switching to warfarin with a target International Normalized Ratio (INR) between 2.0 and 3.0 should be taken into consideration. Conversion from LMWH to VKA should be delayed for at least 5 to 7 days after delivery if a VKA is being considered as an alternative to LMWH therapy during breastfeeding in order to reduce the risk of bleeding during the time when LMWH and VKA treatment are being used concurrently[33] and vitamin K supplementation should be given to the newborn on a regular basis in the first few postnatal weeks[14].Because there are currently no clinical studies on the impact of maternal DOAC therapy on the breastfed child, the manufacturers of these drugs advise against using them in lactating women[75].

Diagnosis of pregnancy-related VTE

To achieve prompt diagnosis and treatment, clinical suspicion for VTE is essential. It should be underlined that LMWH treatment should begin immeditaly when VTE is suspected and delivery is not imminent, rather than waiting to conduct investigations to confirm or rule out the diagnosis[80]. The symptoms and signs of deep venous thrombosis (DVT), particularly lower leg oedema and pain, are non-specific and sometimes mistaken for those of pregnancy especially the lower leg oedema and pain. Because the left iliac vein is usually

compressed by the gravid uterus in symptomatic pregnant women, DVTs are more likely to form on the left leg which increases the likelihood of developing an iliofemoral DVT in the latter stages of pregnancy[80] .

Similarly, the diagnosis of pulmonary embolism (PE) during pregnancy is very challenging since the clinical signs and symptoms of PE typically match physiological changes related to pregnancy. However, PE may be suggested by symptoms such as palpitations, anxiety, pleuritic chest pain, cyanosis, sweating, and cough[76]. The diagnosis of VTE during pregnancy is challenging, as was previously mentioned, primarily because pregnant women do not have the same validated risk factors for VTE as patients who are not pregnant[84] .However, according to the recommendations of the Royal College of Obstetricians and Gynecologists (RCOG), women who exhibit symptoms and signs suggestive of acute PE should have basic tests, such as an ECG and a chest x-ray. Whereas, because D-dimer levels are elevated during normal pregnancy, they do not advise routine testing of D-dimer concentrations[80] .

If PE is suspected along with clinical manifestations of DVT, a compression duplex ultrasound scan of both legs should be done; if the DVT is confirmed, the VTE therapy should continue with no additional testing needed. However, if PE is clinically suspected but there is no clinical suspicion of DVT, either a ventilation/perfusion (V/Q) lungs scan or a CT pulmonary angiography (CTPA) is recommended. The local guidelines, radiology availability, patient and physician preferences, will determine whether V/Q or CTPA is used. In general, CTPA is advised in the event of an abnormal chest x-ray with clinical suspicion of PE, but repeat testing or alternative imaging, is advised in the case of persistent clinical suspicion of PE with normal imaging. Until a PE is objectively ruled out, LMWH should be continued[76].

Similar to non-pregnant patients, the differential diagnosis list for pregnancy-associated DVT includes conditions that present with unilateral swelling, hotness, redness, and tenderness of the lower limb, flank, lower abdomen, buttock, or back, such as Backer's cyst, superficial thrombophlebitis, cellulitis, heterotopic ossification, haematoma, enlarged lymph nodes compressing veins, and muscle tear. The clinical picture of PE during pregnancy, on the other hand, might range from mild dyspnea to shock, and altenative diagnoses could include heart failure, peripartum cardiomyopathy, aortic dissection, pneumothorax, and pneumonia[76].

Treatment strategies for pregnancy-related VTE

Any pregnant woman exhibiting symptoms or signs suggestive of VTE should be reviewed with a senior clinician and/or a haematologist, and anticoagulant medication should be started right once and continued until a diagnosis is conclusively excluded or proven.

A Full Blood Picture, Coagulation Profile, Renal Function Profile, and Liver Function Tests are the baseline blood tests that should be done before beginning anticoagulation; however, thrombophilia screening is unreliable during pregnancy because the results will be influenced by the physiological changes of pregnancy, in addition to the screening results not changing the management plan[76].

Heparins, like thromboprophylaxis in pregnancy, are the recommended therapeutic agents for treating acute VTE episodes in pregnancy with LMWHs preferred, due to their ease of use, predictable anticoagulation effects, and less need for blood level monitoring. Due to the ease with which protamine sulphate can reverse its effects, UFH may be reserved for usage in situations where birth is imminent or in individuals with severe renal impairment. The choices and therapeutic doses of the heparin anticoagulants are shown in Table 1[14].

A multidisciplinary team including a consultant obstetrician, a consultant anaesthetist, a consultant haematologist, and a consultant intensivist should provide immediate and prompt care to patients with massive life-threatening thrombosis in pregnancy. The patient may present in a collapsed or shocked state or in cardiac arrest. The team will determine whether I.V. UFH or thrombolysis is necessary as a life-saving intervention determined on a patient-specific basis.

I.V. UFH is generally advised in cases of massive PE due to its rapid onset of action, whereas thrombolysis may be recommended in patients with life-threatening PE and haemodamically

compromise. Once stability is attained, UFH can be changed into LMWH. However, the risk of complications from maternal and foetal bleeding is only about 2 to 3 %, the same as in individuals who are not pregnant[80].

The management of acute PE during pregnancy may specifically involve inferior vena cava (IVC) filters. However, their usage during pregnancy is restricted due to the hazards involved with the filters' insertion and removal. Risks related to filters may include a mortality rate of 0.12–0.3%, filter migration in >20% of cases, filter breakage in 5% of cases, and IVC perforation in 5% of patients. Temporary caval filters, often referred to as retrievable IVC filters, may be appropriate for women at post partum period, for those who experience recurrent VTE despite receiving adequate treatment, or in cases where anticoagulation is contraindicated[80].

Conflict of interest

The authors declare that they have no conflict of interests.

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