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PREVENTION OF VENOUS THROMBOEMBOLISM IN PREGNANCY

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Abstract: Venous thromboembolic complications (VTE) are a leading causes of maternal mortality in the developed World. To reduce the incidence VTE in pregnancy, and improve outcomes, a wider understanding of the risk factors involved and a better identification of women at risk of thrombosis coupled with effective thromboprophylaxis are required. The common risk factors for VTE in pregnancy are: age over 35 years; obesity; operative delivery (especially emergency Caesarean Section in labour); thrombophilia; and a family or personal history of thrombosis suggestive of an underlying thrombophilia. As warfarin is unsuitable for use in pregnancy because of problems with embryopathy and risk of fetal bleeding, optimal thromboprophylaxis in pregnancy centres on the use of low-molecular-weight heparin (LMWH). There is now extensive experience of the safety and efficacy of LMWH in pregnancy. LMWH's, such as enoxaparin and dalteparin, have clinical and practical advantages compared with unfractionated heparin in terms of improved safety (significantly lower incidence of osteoporosis and heparin induced thrombocytopenia), and patient convenience with once daily dosing for the majority of women. Thus LMWH is now the agent of choice in pharmacological thromboprophylaxis in pregnancy

Key words: pregnancy; thrombosis; thrombophilia; heparin; warfarin; low molecular weight heparin

INTRODUCTION

Pulmonary thromboembolism (PTE) remains a major cause of maternal mortality and is currently the most common direct cause of maternal death in the United Kingdom [1]. PTE arises from deep venous thrombosis (DVT). DVT is associated with a significant risk of recurrent venous thrombosis and deep venous insufficiency, while PTE carries a risk of subsequent pulmonary hypertension. Pregnancy-related VTE may also identify women with an underlying thrombophilia with implications, not only for venous thrombosis, but also for an increased risk of pregnancy complications such as pre-eclampsia and intrauterine growth restriction (IUGR).

In the UK, there is a comprehensive Confidential Enquiry into maternal deaths that has been published every three years since the early 1950's. These reports have shown that the overall incidence of fatal PTE has fallen substantially in the last 40-50 years. However, the greatest reduction in the number of deaths has been those following vaginal delivery, which has probably been related to the 'de-medicalisation' of childbirth with shorter periods of hospitalization after delivery, more rapid mobilization and shorter labours. There remain some areas of concern. In recent years, there has been no further reduction in deaths after vaginal delivery [1] and the number of deaths during the antenatal period have changed little from the early 1950's despite major advances in identification of risk, thromboprophylaxis, diagnosis and therapeutics over this same time period. The total number of deaths following Caesarean Section appears to have fallen sharply since the widespread introduction of specific thromboprophlaxis to UK obstetric practice in the mid-1990's. The need for adequate diagnosis and treatment of thromboembolic disease in pregnancy has been highlighted by the UK Confidential Enquiries into Maternal Deaths [1]. It is clear that many of these deaths are associated with substandard care, including a failure to recognise risk factors for VTE, a failure to provide appropriate thromboprophylaxis for those at risk, a failure to objectively diagnose VTE and a failure to provide appropriate treatment.

The incidence of antenatal DVT has been estimated at 0.615/1000 maternities in women under 35 years of age and at 1.216/1000 maternities in women over 35 years of age [2]. For postpartum DVT, the incidence has been estimated at 0.304/1000 maternities in women under 35 years of age and 0.72/1000 maternities in women over 35 years of age. Although antenatal DVT is more common than postpartum DVT [2,3], the event rate is higher in the puerperium making it the time of greatest risk. Almost 40% of postpartum DVT's present following the woman's discharge from hospital, but complete data on postpartum DVT are difficult to obtain as many cases present to non-obstetric services. Thus, prevention of VTE remains important to contemporary obstetric practice

Risk Factors for Gestational VTE

Specific thromboprophylaxis depends on identifying the level of risk a woman is at. Ideally, such risk assessment should be made pre-pregnancy or in early pregnancy. The common risk factors for VTE in pregnancy are: age over 35 years; obesity; operative delivery (especially emergency Caesarean Section in labour); thrombophilia; and a family or personal history of thrombosis suggestive of an underlying thrombophilia [4]. Additional risk factors are shown in Table 1.

Table 1. Common Risk Factors for VTE in Pregnancy.

Patient factors
Age over 35 years
Obesity (BMI > 29kg/M^2) in early pregnancy
Thrombophilia
Past history of VTE (especially if idiopathic or thrombophilia associated)
Gross varicose veins
Significant current medical problem (eg nephrotic syndrome)
Current infection or inflammatory process (eg active inflammatory bowel disease or urinary tract infection)
Immobility (eg. bed rest or lower limb fracture)
Paraplegia
Recent long distance travel
Dehydration
Intravenous drug abuse
Ovarian hyperstimulation
Pregnancy/Obstetric factors
Caesarean section particularly as an emergency in labour
Operative vaginal delivery
Major obstetric haemorrhage
Hyperemesis gravidarum
Pre-eclampsia
Caesarean section particularly as an emergency in labour

An often overlooked area is the risk of VTE associated with ovarian hyperstimulation, which is associated with procoagulant changes in the haemostatic and fibrinolytic systems [5]. As many as 1%-2% of conceptions assisted by IVF can be complicated by severe hyperstimulation. Both venous and arterial thrombosis can occur, but the absolute rate is low. Interestingly, when VTE occurs with hyperstimulation, it is usually located in the internal jugular vein presenting with neck pain and swelling [6]. There may be an association with underlying thrombophilia where the risk of VTE may be substantial. Thus, a risk assessment for thrombosis should be undertaken in women undergoing assisted conception therapy and appropriate thromboprophylaxis should be provided for those at risk.

Longterm Morbidity from Gestational VTE

Previous VTE is associated with an increased risk of future VTE. There is also a risk of deep venous insufficiency developing: 80% of women with VTE develop post-thrombotic syndrome and over 60% will have objectively confirmed deep venous insufficiency following a treated DVT [7]. The risk of developing venous insufficiency after DVT is greater than with PTE (odds ratio 10.9 [95% CI 4.2-28.0] for DVT compared to 3.8 [95% CI 1.2-12.3]) after PTE [7]. This may be due to the clot clearing from the leg veins in those with PTE leading to less extensive damage to the deep venous system. This is a significant problem. Berqvist et al. [8] reported that up to 21% of women with a treated DVT in pregnancy required to use a compression bandage and 6% had venous ulcers at a median time of follow-up of 10 years. Historical data show rates for venous ulceration following untreated DVT to be 19%-28% on follow-up periods ranging from 6-31 years [8].

Pathophysiological Mechanisms in Gestational VTE

Virchow's triad of hypercoagulability, venous stasis and vascular damage, all occur in the course of uncomplicated pregnancy. Plasma levels of coagulation factors such as von Willebrand factor, Factor VIII, and fibrinogen increase substantially. Almost 40% of pregnancies acquire resistance to the endogenous anticoagulant, activated protein C, and a reduction in protein S, the co-factor for protein C is seen in normal pregnancy [9]. Fibrinolysis is inhibited by increased levels of plasminogen activator inhibitors 1 and 2, the latter being derived from the placenta [10]. As high levels of Factor VIII and resistance to activated protein C have been associated with an increased risk of VTE in the non-pregnant, these physiological changes may explain, at least in part, the increased risk of VTE in pregnancy. Relative venous stasis, measured by ultrasound, also occurs in pregnancy with around a 50% reduction in venous flow velocity by 25-29 weeks' gestation, reaching a nadir at 36 weeks [11] and taking around 6 weeks to return to normal non-pregnant flow rates [12]. Finally, some degree of endothelial damage to pelvic vessels appears inevitable during the course of vaginal or abdominal delivery.

Interestingly, almost 90% of pregnancy-associated DVT occur on the left side in contrast to the non-pregnant situation, where only 55% of DVT occur on the left [4, 13]. This may reflect some compression of the left iliac vein by the right iliac artery and the ovarian artery, which cross the vein on the left side only. More impor-

tantly, perhaps, around 70% of gestational DVT are ileo-femoral in their location. This contrasts with around a 9% rate of ileofemoral DVT in the non-pregnant, where calf vein DVT predominate. As ileo-femoral DVT are more likely to embolise than calf vein thrombosis, this is an important consideration.

Thrombophilia and Gestational VTE

One or more heritable or acquired thrombophilias are now found in at least 50% of cases of VTE in pregnancy. The main heritable thrombophilias recognized currently include deficiencies of the endogenous anticoagulant proteins, antithrombin, Protein C and Protein S and abnormalities of pro-coagulants, particularly Factor V Leiden and the prothrombin gene variant (prothrombin G20210A).

Deficiencies of antithrombin, protein C and protein S, where the major components of the body's endogenous anticoagulant system are defective or deficient due to quantitative or qualitative defects are uncommon. They have a combined prevalence of less than 1% [14]. Investigation of gestational VTE will reveal one of these defects in less than 10% of cases.

Factor V Leiden is functionally manifest as resistance to activated Protein C, the endogenous anticoagulant that inactivates Factor Va and Factor VIIIa by proteolytic cleavage. Resistance is due to a single point mutation in the Factor V gene, which leads to an alteration in Factor V at the activated protein C cleavage site (Arg 506). This results in a potentially hypercoagulable effect as the activated Factor V cannot be broken down by activated protein C. Factor V Leiden occurs in 2% - 7% in Western European populations [14], and will usually be identified in 20%-40% of women with VTE [15]. Activated protein C resistance can also be seen with other thrombophilic problems such as antiphospholipid antibody syndrome and genetic abnormalities in Factor V other than Factor V, such as Factor V Cambridge or the HR2 haplotype. Although defects such as FV Cambridge are uncommon, the HR2 haplotype is relatively common and has been reported to carry an excess risk of VTE in patients with a high risk profile (OR1.8 95%CI1.1-2.8) including pregnancy [16]. It is of interest that, although Factor V Leiden is associated with an increase in risk of VTE, this is largely due to DVT. Outwith pregnancy, the prevalence of underlying Factor V Leiden in PTE is around half of that for DVT [17]. This differs from other thrombophilias such as prothrombin G20210A where there is no difference in the underlying prevalence between DVT and PTE. The mechanism is not clear. It has been proposed that Factor V Leiden is associated with a more adherent and stable thrombus, possibly due to increased local thrombin generation, so reducing the likelihood of embolisation. Whether this applies in pregnancy to women with Factor V Leiden is not yet clear.

Prothrombin G20210A, occurs in the heterozygous form in about 2% of Western European populations. This genotype is expressed as elevated plasma prothrombin levels. It appears to increase the risk of venous thrombosis by a factor of three [18]. Prothrombin G20210A can be found in around 6% of patients with VTE and has been reported in almost 20% of those with a strong family history of VT E [18]. Gestational VTE has been linked to this genotype [19,20].

It is noteworthy that the FV Leiden and prothrombin G20210A genotypes do not occur with similar frequencies in all populations. For example, in the Taiwan Chinese, Factor V Leiden and prothrombin G20210A was found in only 0.2% of the population compared with 4.8% and 1.2% respectively in a control population of Newfoundlanders [21].

Hyperhomocysteinaemia has been linked to VTE in the non-pregnant situations [22]. Hyperhomocysteinaemia can be associated with homozygosity for a variant of the methylene-tetrahydrofolate reductase gene (MTHFR C677T). This genotype, itself, is not directly linked to venous thrombosis, but predisposes to arterial and venous thrombosis where there is concomitant B vitamin deficiency. Around 10% of individuals in Western European populations are homozygous for this common genetic variant. However, such homozygotes do not appear to be at increased risk of pregnancy-related VTE [19, 23, 24]. The reason for this is unclear, but as clinical events in homozygotes are likely to reflect the interaction of the genotype with a relative deficiency of B vitamins such as folic acid, the absence of an association of this genotype with gestational VTE may reflect the pregnancy-related physiological reduction in homocysteine levels and/or the effects of folic acid supplements that are now taken widely by women in pregnancy.

Heritable thrombophilic abnormalities are common, affecting at least 15% of Western populations [25, 26] and underlie around 50% of gestational VTE, yet only around 1:1,000 pregnancies are complicated by a VTE. Thus, thrombophilia alone, even in conjunction with the gestational changes in haemostasis and thrombosis, does not invariably lead to thrombosis. This is because clinical thrombosis in women with thrombophilia is a multicausal event resulting from the interaction between congenital and acquired risk factors [26]. The likelihood of thrombosis depends on the thrombophilia, whether more than one thrombophilia is present, whether previous VTE have occurred, and additional risk factors, such as obesity.

It is important to consider the level of risk for thrombosis during pregnancy in women with thrombophilia to guide thromboprophylaxis. Several recent studies have provided estimates for the risk of gestational thrombosis in the more common thrombophilias [4, 19, 24, 27, 28, 29, 30, 31, 32, 33] and results from several of these studies are shown in Table 2.

Table 2. Risk of VTE in Pregnancy with Thrombophilia.

Thrombophilic Defect	Odds Ratio (95% CI) for VTE in Pregnancy*	Relative Risk (95% CI) for VTE in Pregnancy**	Relative Risk (95% CI) for VTE in Pregnancy or Puerperium ***
AT deficiency Type 1 (quantitative deficiency)	282 (31-2532)	N/a	N/a
AT deficiency Type 2 (qualitative deficiency)	28 (5.5-142)	N/a	N/a
AT deficiency (activity < 80%)	N/a	10.4 (2.2-62.5)	N/a
F V Leiden heterozygotes	4.5 (2.1-14.5)	6.9 (3.3-15.2)	8.7 (3.4-22.5)
Prothrombin 20210A heterozygotes	4.4(1.2-16)	9.5 (2.1-66.7)	1.8 (0.6-5.4)
MTHFR C677T homozygotes	0.45 (0.13-1.58)	No increase in risk (RR not reported)	N/a
Any thrombophilia	N/a	N/a	9.0 (4.7-17.1)
Antithrombin, protein C or protein S deficiency (not adjusted for parity)	N/a	N/a	13.1 (5.0-34.5)

* Based on a retrospective study of 93,000 pregnancies where odds ratios were calculated by screening women with VTE in pregnancy for thrombophilia and relating this to the known prevalence of these defects in the population [34].

** Based on a study of 119 women with thromboembolism in pregnancy and 233 controls for the presence of congenital thrombophilia [34]. Relative risk calculated after logistic regression to adjust for age, body mass index, oral contraceptive use, protein C and S activity, Factor V Leiden, prothrombin G20210A, MTHFR 677TT and antithrombin activity.

*** Based on a case control study of 119 cases who had a first episode of objectively confirmed VTE in pregnancy or the puerperiumand 232 controls. Relartive risk adjusted for parity. No difference between relative risk in pregnancy or puerperium found [29].

Table 3. Cost Effectiveness of Screening for Factor V Leiden in Pregnancy [36].

	No Screening (n = 967)	Selective screening (n = 113)	Universal screening (n = 967)
Cost of screening for mutation	0	£1,305.31	£11,543.29
Cost of prophylactic postpartum LMWH for those positive for FVL	0	£595.48	£5,959.80
Cost of prophylactic LMWH (from 12-40 weeks gestation) for those positive for FVL	0	£2,774.94	£27,787.20
Averted costs of treating vascular events (assumes 50% reduction with prophylaxis)	0	£908.13	£5,448.81
Net cost of treatment for whole cohort	£158,013.4	£157,105.3	£152,566.6
Total cost of management strategy	£158,013.4	£161,781.0	£197,856.9
Number identified with FVL	0	3	30
Number with complications associated with FVL	87	1	6
Events prevented by screening (assumes 50% reduction with prophylaxis)	0	0.5	3

Combined defects substantially increase risk with an odds ratio estimated at 107 for the combination of factor V Leiden and prothrombin G20210A. Homozygotes for defects such as Factor V Leiden also have a greater level of risk than heterozygotes. For example the absolute risk of VTE with homozygous Factor V Leiden has been reported to be 9.5% (95% CI 6-149 [35].

These data are valuable in evaluating risk and advising women whether to use thromboprophylaxis in pregnancy.

At present, there is no evidence to support universal screening for thrombophilia in pregnancy, either for the prevention of VTE, or pregnancy complications. The natural history of many of these thrombophilias, particularly in asymptomatic kindred, is not yet established, appropriate intervention is unclear, and cost effectiveness is not established. A recent study has shown that universal screening for Factor V Leiden in pregnancy is not cost effective [36].

Selective screening of women with VTE in pregnancy, or who have a personal or family history of, ideally, objectively confirmed, VTE, may be of value as around 50% of such women will have a heritable thrombophilia. There is consensus that women with a personal history of VTE and an underlying thrombophilia should receive thromboprophylaxis with low molecular weight heparin (LMWH) during pregnancy and with LMWH or coumarin in the puerperium [37]. Screening for thrombophilia in patients with problems such as recurrent miscarriage, intrauterine death, intrauterine growth restriction and severe pre-eclampsia, which may all reflect an underlying thrombophilia and, therefore, risk of VTE, should also be considered [25]. However, apart from recurrent miscarriage associated with antiphosphlipid antibody syndrome, effective intervention is not established. Nonetheless, if these women have a thrombophilia that is symptomatic in relation to a pregnancy complication, they may also be at risk of venous thrombosis due to the presence of multiple risk factors including a thrombophilia, or a severe thrombophilia such as antithrombin deficiency, conditions which would, themselves, merit specific thromboprophylaxis. As in any screening situation, appropriate counselling should be offered.

Antithrombotic Therapy in Pregnancy

Prophylaxis of gestational VTE centres on the use of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) due to the fetal hazards of warfarin [38]. Although warfarin is not secreted in breast milk in clinically significant amounts and is safe to use during lactation, it crosses the placenta and is a known teratogen. Warfarin embryopathy consists of midface hypoplasia, stippled chondral calcification, scoliosis, short proximal limbs and short phalanges. It may occur with exposure to the drug between 6 and 9 weeks' gestation. It is during this period that the nasal septum more than doubles in length. In a rat model, ectopic calcification occurs in the septal cartilage, causing a reduction in the longitudinal growth of the nasal septum and associated maxillonasal hypoplasia, so illustrating the causative link [39]. The characteristic nasal hypoplasia can be corrected with plastic surgery techniques [40]. The incidence of this condition has been estimated at around 5% [38]. This problem is potentially preventable by substitution of heparin for warfarin during the first trimester. The risk of embryopathy may be dose dependent, as an increased risk has been reported when the dose of warfarin is greater than 5mg/day [41]. In addition to warfarin embryopathy, there is the possibility of problems arising due to fetal bleeding. As the fetal liver is immature and levels of Vitamin K dependant coagulation factors low, maternal warfarin therapy maintained in the therapeutic range, will be associated with excessive anticoagulation and, therefore, potential haemorrhagic complications in the fetus. Furthermore, recent data show that prenatal exposure to coumarins is associated with an increased risk of disturbance in development manifest as minor neurological dysfunction, or a low intelligence quotient in schoolage children, with a relative risk of 7.6 for two or more of these minor abnormalities [42]. Warfarin should be avoided around the time of delivery and, therefore, is usually stopped at around 36 weeks' gestation [38, 43], or earlier, if preterm delivery is planned or expected, because of the excessive haemorrhagic risk to both mother and fetus.

Neither UFH [42] nor LMWH cross the placenta [44, 45] as determined by measuring anti-Xa activity in fetal blood, and there is no evidence of teratogenesis or risk of fetal haemorrhage. On systematic review, LMWHs appear safe for the fetus [46]. Heparins are not secreted in breast milk and can be used during breast feeding. Prolonged use of UFH is associated with symptomatic osteoporosis, with around a 2% incidence of osteoporotic fractures, allergy and heparin-induced thrombocytopenia [47]. However, LMWH appears to have a substantially lower risk of osteoporosis. A recent randomised trial of UFH or dalteparin for thromboprophylaxis in pregnancy, measured bone mineral density in the lumbar spine for up to 3 years after delivery [48]. Bone density did not differ between healthy controls and the dalteparin group, but was significantly lower in the UFH group when compared to both controls and dalteparin-treated women. Multiple logistic regression found that the type of heparin therapy was the only independent factor associated with reduced bone mass. Heparin-induced thrombocytopenia is uncommon but, nonetheless, important. It is an idiosyncratic immune reaction associated with extensive venous thrombosis. It usually occurs between 5 and 15 days after starting heparin. The risk is around 1%-3% with unfractionated heparin and is substantially lower, indeed negligible, with low molecular weight heparin [49]. Allergic reactions usually take the form of itchy, erythematous lesions at the injection sites. Changing the heparin preparation may be helpful but cross reactivity can occur [50]. Allergic reactions should be distinguished from faulty injection technique with associated bruising. LMWH is now the heparin of choice in pregnancy because of a better side effect profile, good safety record for mother and fetus and convenient

once daily dosing for prophylaxis [46, 51, 52, 53, 54, 55, 56]. Almost 1500 cases of prophylaxis or treatment of VTE in pregnancy with enoxaparin and dalteparin, the two most commonly reported LMWHs in pregnancy, have now been reported in the literature and the risk of recurrent VTE is around 1.2% and of symptomatic osteoporotic fracture 0.007% (unpublished data).

Hirudin, a direct thrombin inhibitor, is used in the non-pregnant for treatment of heparin-induced thrombocytopaenia, and has also been used successfully for postoperative thromboprophylaxis as an alternative to heparin. As it crosses the placenta, it is probably best avoided in pregnancy, although there are case reports of its use in women with heparin-induced thrombocytopaenia. In one report, it was successfully used in a pregnant woman with systemic lupus erythematosus and recurrent venous thromboembolism who suffered from heparin-induced thrombocytopenia while treated with dalteparin and who also cross reacted with danaparoid. Anticoagulation with 15mg subcutaneous r-hirudin was performed twice daily from the 25th week of pregnancy until delivery. No thromboembolism or bleeding or fetal toxicity of r-hirudin was detected [57]. It has also been used in a lactating mother because of heparin-induced thrombocytopaenia and hirudin was not detectable in breast milk [58]. As it is a protein of non-human origin, it is potentially immunogenic and antihirudin antibodies have been reported in over 40% of patients with heparin-induced thrombocytopenia (HIT) who received lepirudin as parenteral anticoagulation for 2 to 10 days [59]. Development of these antibodies is related to the duration of treatment. Further, they will enhance the activity of lepirudin and so, during prolonged treatment with lepirudin, anticoagulant activity should be monitored to avoid bleeding complications.

Dextran has been used for peripartum thromboprophylaxis, particularly, during Caesarean Section. It carries a significant risk of anaphylactic and anaphylactoid reactions. There is a risk of maternal anaphylactoid reactions which have been associated with uterine hypertonus, profound fetal distress, and a high incidence of fetal death or profound neurological damage [60]. Thus, Dextran for thromboprophylaxis should be avoided prior to delivery.

Graduated elastic compression stockings (GECS) are effective in the non-pregnant and, in view of the pregnancy-related changes in the venous system, should be of value in pregnancy and post-partum. The mechanism of action of GECS may act by preventing overdistension of the leg veins so preventing endothelial damage and exposure of subendothelial collagen with subsequent activation of the coagulation system [61]. Other mechanical techniques, such as intermittent pneumatic compression, are of value during Caesarean Section and immediately postpartum for prophylaxis.

Aspirin has been found in meta-analysis to have a beneficial effect in the prevention of DVT. Its effectiveness for VTE prophylaxis in pregnancy, in comparison with heparin, remains to be established, but it is likely to offer some benefit. Its effectiveness is likely to be less than that of heparin and LMWH [62]. In women who are unable to take heparin or, in whom the balance of risk is not considered sufficient to merit heparin, it may be useful. Low dose (60-75mg daily) aspirin is not associated with adverse pregnancy outcome in the second and third trimesters [63, 64].

Thromboprophylaxis in Pregnancy

The management of the woman with a single previous VTE has been controversial until recently. This was because of the wide variation in risk that has been reported (1%-13%) [37, 65, 66, 67, 68] and concerns about the hazards of longterm unfractionated heparin therapy, particularly, osteoporosis. The higher estimate of risk led many clinicians to employ pharmacological prophylaxis with heparin or low molecular weight heparin during pregnancy and the puerperium. However, these estimates of risk have significant limitations. For example, objective testing was not used in all cases, some of the studies were retrospective and the prospective studies had relatively small sample sizes. Brill-Edwards et al. [69] reported a prospective study of 125 pregnant women with a single previous objectively diagnosed VTE. No heparin was given antenatally but anticoagulants, usually warfarin following an initial short course of heparin or low molecular weight heparin (LMWH), was given for four to six weeks post-partum. The overall rate for recurrent antenatal VTE was 2.4% (95%CI 0.2 to 6.9). Interestingly, none of the 44 women (95% CI 0.0 to 8.0) who did not have an underlying thrombophilia and whose previous VTE had been associated with a temporary risk factor, developed a VTE, while 5.9% (95%CI 1.2-16%) of the women who were found to have an underlying thrombophilia or whose previous VTE had been idiopathic, had a recurrent event. As pregnancy is associated with hyper-estrogenism, this should probably be considered a recurrent risk factor in women with a previous VTE on the "pill" or in pregnancy.

Thus, in the woman with a previous VTE that was not pregnancy-related, associated with a risk factor that is no longer present and with no additional risk factor or underlying thrombophilia, antenatal LMWH should not be routinely prescribed, but this strategy must be discussed with the woman and her views taken into account, especially in view of the wide confidence intervals reported by Brill-Edwards et al. (95% CI 0-8.0%). Graduated elastic compression stockings and/or low dose aspirin can be employed antenatally in these women. Postpartum, she should receive anticoagulant therapy for at least 6 weeks (eg. 40mg enoxaparin or 5000iu dalteparin daily or warfarin (target INR 2-3) with LMWH overlap

Table 4. Suggested Management Strategies for Various Clinical Situations. (NB. specialist advice for individualised management of patients is advisable in many of these situations).

Clinical Situation	Suggested Management
Single previous VTE (not pregnancy or 'pill' related) associated with a transient risk factor and no additional current risk factors, such as obesity.	*Antenatal:* surveillance or prophylactic doses of LMWH (eg 40mg enoxaparin or 5000iu dalteparin daily), ± graduated elastic compression stockings. Discuss decision regarding antenatal LMWH with the woman. *Postpartum:* anticoagulant therapy for at least 6 weeks (eg 40mg enoxaparin or 5000iu dalteparin daily or warfarin (target INR 2-3) with LMWH overlap until the INR is > 2.0.) ± graduated elastic compression stockings.
Single previous *idiopathic* VTE or single previous VTE with underlying thrombophilia and not on long-term anticoagulant therapy, or single previous VTE and additional current risk factor(s) (eg morbid obesity, nephrotic syndrome).	*Antenatal:* prophylactic doses of LMWH (eg 40mg enoxaparin or 5000iu dalteparin daily) ± graduated elastic compression stockings. NB: there is a strong case for more intense LMWH therapy in antithrombin deficiency (e.g. enoxaparin 0.5-1mg/kg 12 hourly or dalteparin 50-100 IU/kg 12 hourly). *Postpartum:* anticoagulant therapy for at least 6 weeks (eg 40mg enoxaparin or 5000iu dalteparin daily or warfarin (target INR 2-3) with LMWH overlap until the INR is > 2.0.) ± graduated elastic compression stockings.
More than one previous episode of VTE, with no thrombophilia and not on long-term anticoagulant therapy	*Antenatal:* prophylactic doses of LMWH (eg 40mg enoxaparin or 5000iu dalteparin daily) + graduated elastic compression stockings. *Postpartum:* anticoagulant therapy for at least 6 weeks (eg 40mg enoxaparin or 5000iu dalteparin daily or warfarin (target INR 2-3) with LMWH overlap until the INR is > 2.0.) + graduated elastic compression stockings.
Previous episode(s) of VTE in women receiving long-term anticoagulants (eg with underlying thrombophilia)	*Antenatal:* switch from oral anticoagulants to LMWH therapy (e.g. enoxaparin 0.5-1mg/kg 12 hourly or dalteparin 50-100 IU/kg 12 hourly) by 6 weeks gestation + graduated elastic compression stockings. *Postpartum:* resume long-term anticoagulants with LMWH overlap until INR in pre-pregnancy therapeutic range + graduated elastic compression stockings..
Thrombophilia (confirmed laboratory abnormality) but no prior VTE.	*Antenatal:* surveillance or prophylactic LMWH ± graduated elastic compression stockings. The indication for pharmacological prophylaxis in the antenatal period is stronger in AT deficient women than the other thrombophilias, in symptomatic kindred compared to asymptomatic kindred and also where additional risk factors are present. *Postpartum:* anticoagulant therapy for at least 6 weeks (eg 40mg enoxaparin or 5000iu dalteparin daily or warfarin (target INR 2-3) with LMWH overlap until the INR is > 2.0.) ± graduated elastic compression stockings.
Following caesarean section or vaginal delivery.	Carry out risk assessment for VTE. If additional risk factors such as emergency section in labour, age over 35 years, high BMI etc present then consider LMWH thromboprophylaxis (eg 40mg enoxaparin or 5000iu dalteparin) ± graduated elastic compression stockings.

until the INR is > 2.0.) ± graduated elastic compression stockings. (Table 4).

In those women with a single previous VTE and an underlying thrombophilia, or where the VTE was idiopathic or pregnancy- or "pill" –related, or where there are additional risk factors such as obesity or nephrotic syndrome, there is a stronger case for LMWH prophylaxis. Antenatally, these women should be considered for prophylactic doses of LMWH (eg. 40mg enoxaparin or 5000iu dalteparin daily) ± graduated elastic compression stockings. This should be started as soon

as possible following the diagnosis of pregnancy. More intense LMWH therapy in the presence of antithrombin deficiency is usually prescribed (eg. enoxaparin 0.5-1mg/kg 12 hourly or dalteparin 50-100 IU/kg 12 hourly), although many women with previous VTE and antithrombin deficiency will be on longterm anticoagulant therapy (see below). Postpartum anticoagulant therapy for at least 6 weeks (eg. 40mg enoxaparin or 5000iu dalteparin daily or warfarin (target INR 2-3) with LMWH overlap until the INR is > 2.0.) ± graduated elastic compression stockings is recommended. (Table 4).

In the woman with multiple previous VTE, and no identifiable thrombophilia and who is not on longterm anticoagulant therapy, there is consensus that she should receive antenatal LMWH thromboprophylaxis (eg. 40mg enoxaparin or 5000iu dalteparin daily) and graduated elastic compression stockings. This should be started as soon as possible following the diagnosis of pregnancy. Post-partum she should receive at least 6 weeks pharmacological prophylaxis, either with low molecular weight heparin, or warfarin. If she is switched to warfarin postpartum, the target INR is 2-3 and LMWH should be continued until the INR is ≥ 2. A longer duration of postpartum prophylaxis may be required for women with additional risk factors.

When prophylactic doses of LMWH are used, the dose may require to be reduced in women with very low or very high body weight. At low body weight (< 50kg or BMI less than 20kg/M^2), lower doses of LMWH may be required (eg. 20mg enoxaparin daily or 2500iu dalteparin daily), while in obese patients, (eg. BMI > 30 in early pregnancy), higher doses of LMWH may be required. The platelet count should be checked before, and one week after, the introduction of LMWH, then on around a monthly basis to detect heparin-induced thrombocytopenia [70].

The woman with previous episode(s) of VTE receiving longterm anticoagulants (eg. with underlying thrombophilia) should switch from oral anticoagulants to LMWH by 6 weeks' gestation, and be fitted with graduated elastic compression stockings. These women should be considered at very high risk of antenatal VTE and should receive anticoagulant prophylaxis throughout pregnancy. They should be advised, ideally, pre-pregnancy, of the need to switch from warfarin to LMWH as soon as pregnancy is confirmed. The dose of heparin given should be closer to that used for the treatment of VTE rather than that used for prophylaxis (eg. enoxaparin 0.5-1mg/kg 12 hourly or dalteparin 50-100 IU/kg 12 hourly. NB. 12 hourly injections may be preferable to once daily injections in view of the increased clearance of LMWH in pregnancy), based on the early pregnancy weight [70]. The platelet count should be checked before, and one week after, the introduction of LMWH, then around monthly, although HIT is extremely unlikely to occur. Postpartum, she should resume longterm anticoagulants with LMWH overlap until INR is in the pre-pregnancy therapeutic range, plus graduated elastic compression stockings.

Where a woman has thrombophilia confirmed on laboratory testing, but no prior VTE, surveillance or prophylactic LMWH ± graduated elastic compression stockings can be used antenatally. The indication for pharmacological prophylaxis in the antenatal period is stronger in AT deficient women (where dose of LMWH of enoxaparin 0.5-1mg/kg 12 hourly or dalteparin 50-100 IU/kg 12 hourly are usually employed), than the other thrombophilias and also in symptomatic kindred compared to asymptomatic kindred. The presence of additional risk factors, eg. obesity or immobility, may also merit consideration for antenatal thromboprophylaxis with LMWH. Postpartum, these women should receive anticoagulant therapy for at least 6 weeks (eg. 40mg enoxaparin or 5000iu dalteparin daily or warfarin (target INR 2-3) with LMWH overlap until the INR is ≥ 2.0.) ± graduated elastic compression stockings. These women usually require specialised and individualised advice form clinicians with expertise in the area.

Women undergoing Caesarean Section and vaginal delivery should also have a risk assessment for VTE [52]. In a patient undergoing Caesarean Section, thromboprophylaxis (eg 40mg enoxaparin or 5000iu dalteparin) should be prescribed if she has one or more additional risk factors, such as emergency Section in labour, age over 35 years, high BMI. In patients at high risk, graduated elastic compression stockings should be used. These can also be employed if heparin is contraindicated. In women undergoing vaginal delivery, a similar strategy can be used with LMWH being prescribed if there are 2 or more additional minor risk factors or one major risk factor eg. morbid obesity [1].

There has been concern with regard to LMWH and epidural haematoma, through post marketing reports to the FDA largely from the USA. These events have mostly been in elderly women (median age 75 years) undergoing orthopaedic surgery. Additional factors such as concomitant nonsteroidal anti-inflammatory agent use (which can enhance bleeding risk particularly in the elderly) or multiple puncture attempts at spinal or epidural have also been implicated. The true incidence of epidural haematoma is impossible to determine due to lack of denominator data. In addition, practice in North America and Europe may differ, particularly, with regard to LMWH use. In Europe, enoxaparin is used in a dose of 20mg or 40mg daily, while in North America, 30mg twice daily, may be used. Such differences in patients and practice make it difficult to extrapolate the information in these reports to obstetric practice. A degree of caution must, nonetheless, be exercised in the concomitant use of LMWH and neuraxial anaesthesia. In general terms, neuraxial anaesthesia is not used until at least 12 hours after the previous prophylactic dose of LMWH. When a woman presents whilst on a therapeutic regimen of LMWH, regional techniques should not be em-

ployed for at least 24 hours after the last dose of LMWH. LMWH should not be given for at least three hours after the epidural catheter has been removed and the cannula should not be removed within 10-12 hours of the most recent injection [71, 72, 73].

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