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Thromboprophylaxis in pregnant patient-specific risks

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Abbreviation:
VTE – venous thromboembolism
DVT – deep vein thrombosis
PAI-1 – plasminogen activator inhibitor type 1
PAI-2 – plasminogen activator inhibitor type 2
F I – Factor I
F II – Factor II
F VII – Factor VII
F VIII – Factor VIII
F IX – Factor IX
F X – Factor X
FVL – Factor V Leiden
AT – Antithrombin deficiency
UFH – unfractionated heparin
LMWH – low-molecular-weight-heparin
HIT – heparin-induced thrombocytopenia

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Abstract

***Background**: Pregnancy and the puerperium are well-established risk factors for venous thromboembolism. Prothrombotic changes start after conception and normal coagulation returns eight weeks after the labour. The risk of DVT is approximately twice as high after caesarean delivery than vaginal birth.*

***Specific risks:** Inherited or acquired thrombophilias increase thromboembolic risk and influence the approach to thromboprophylaxis. Additional factors that increase thrombotic risk include immobilisation, such as bed rest for pregnancy complications, surgery including caesarean section, ovarian hyperstimulation during gonadotropin use for in vitro fertilisation, trauma and malignancy. The preferred agents for thromboprophylaxis in pregnancy are heparin compounds; these agents do not cross the placenta and therefore appears safe for the fetus. Because of the theoretical risk of epidural spinal haemorrhage in women receiving heparin that undergo epidural or spinal anaesthesia many anaesthesiologist will not perform neuraxial regional anaesthesia in women who have recently received heparin. Anaesthesia guidelines advise waiting to insert the needle at least 10 to 12 hours after the last prophylactic dose of LMWH, and at least 24 hours after the last therapeutic dose.*

***Conclusion:** Despite the increased risk of thrombosis in pregnancy, anticoagulants are not routinely indicated, because the risks usually outweigh the benefits. The exception is women on life-long anticoagulation or women with history of thrombosis or thrombophylia. Heparin therapy must be interrupted temporarily during the immediate peripartum interval to minimise the risk of haemorrhage and to allow for the option of regional anaesthesia.*

INTRODUCTION

Uteroplacental circulation is essential for normal pregnancy development. The coagulation system undergoes significant changes during pregnancy. The clinician caring for the parturient must understand these changes, particularly when the parturient must has a pre-existing haematological condition. Prothrombotic changes start after conception and normal coagulation returns eight weeks after the labour. So, pregnancy and the puerperium are well-established risk factors for venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Incidence of VTE is 4 to 50 times higher in pregnant versus non-pregnant women, with absolute incidence rate of 1 in 500 to 2000 pregnancies. VTE is nearly twice more often postpartum than antepartum, and DVT is three times more common than pulmonary embolism *(1)*. In developed countries, while

mortality from other causes has been reduced and haemorrhage is successfully treated or prevented, VTE has emerged as leading cause of maternal death *(2)*.

The risk of DVT is approximately twice as high after caesarean delivery than vaginal birth, and DVT is more common in the left than the right leg. The striking distribution is attributed to increased venous stasis in the left leg related to compression of the left iliac vein by the right iliac artery, coupled with compression of the inferior cava by the gravid uterus itself. Pelvic vein DVT is felt to be more likely in pregnancy, perhaps making diagnosis more difficult.

Coagulation disorders in pregnancy

Pregnancy and the postpartum period may be marked by the presence of all three components of Virchow's triad: venous stasis, endothelial injury and a hypercoagulable state. Inherited or acquired thrombophilias unrelated to pregnancy increase thromboembolic risk and influence the approach to thromboprophylaxis. Venous stasis of the lower extremitas occurs because of two factors; pregnancy-associated changes in venous capacitance and compression of large veins by the gravid uterus. Although blood volume and total venous return are supranormal in pregnancy, the linear flow velocity in the lower extremity veins is decreased, probably due to hormonal induced dilatation of capacitance veins, which leads to venous pooling and valvular incompetence. Assuming the left lateral position significantly increased the velocity in both lower extremities. Endothelial injury is connected with delivery, which is associated with vascular injury and changes at the uteroplacental surface *(3)*. Furthermore, pregnancy is a hypercoagulable state with increased several coagulation factors; F I, II, VII, VIII, IX and X, with a lower levels of protein S and increased resistance to activated protein C. Plasminogen activator inhibitor type 1 (PAI-1) levels are fivefold increased and levels of PAI-2, produced by the placenta, dramatically increase during the third trimester, however total fibrinolytic activity may not be impaired *(4)*.

Risk factors for VTE

Inherited thrombophilia is present in 30–50% women with pregnancy-associated VTE. Pregnant women with inherited thrombophilias have even more increased risk for VTE.

The thrombotic risk for women with factor V Leiden during pregnancy or in puerperium has been estimated at approximately 1 in 400 to 500 *(5)*. Not only are women with thrombophilia at a higher risk of thrombosis, they are more likely to experience placental abruption, preeclampsia, fetal growth restriction, still-birth and possibly recurrent miscarriage. Factor V Leiden (FVL) is the most frequently indentified inherited thrombophilia. Thrombophilia associated with a high risk of VTE during pregnancy include AT deficiency, protein C or S deficiency, compound heterozygosity for FVL and prothrombin gene mutation or other combinations of thrombophilia, and homozygosity for these conditions. Acquired antithrombin deficiency may also occur in high-proteinuric states such as nephritic syndrome or preeclampsia, further increasing thrombotic risk.

Additional factors that increase thrombotic risk include immobilisation, such as bed rest for pregnancy complications, surgery including caesarean section, ovarian hyperstimulation during gonadotropin use for in vitro fertilisation, trauma, malignancy and hereditary or acquired hypercoagulable states. Other conditions that increase thrombotic risk include hyperemesis gravidarum, obesity, inflammatory bowel disease, infection, smooking and indwelling intravenous catheter *(6)*.

The goal of anticoagulation is not only to prevent and treat maternal thromboses, but to improve the outcome of pregnancy. In women with a history of thrombosis and thrombophilia, anticoagulants have been shown to reduce maternal morbidity and mortality. In women with the antiphospholipid syndrome, an aquired thrombophilia and women with inherited thrombophilia anticoagulants have been shown to increase the probability of a live birth *(7)*.

Anticoagulants in pregnancy

Anticoagulation in pregnancy requires consideration of both mother and fetus. During pregnancy there is an increase in blood volume of 40% to 50% and an increase in the volume of distribution. An increase in glomerular filtration results in increased renal excretion. Additionally, there is an increase in protein binding of heparin. Agents that cross the placenta are potentially teratogenic.

Warfarin is a vitamin K antagonist. The coagulant activity of factors II, VII, IX and X depends of vitamin K. Treatment with warfarin results in the production of coagulation factors with reduced coagulant activity. Warfarin is generally contraindicated during pregnancy. Taken during the critical period of organogenesis, warfarin carries up to a 30% risk of congenital anomalies. The reported risk of miscarriage ranges from 14.6% to 56%. Placental transfer of warfarin later in pregnancy can result in fetal bleeding or stillbirth *(8)*. Long term neurologic damage has been reported among children exposed in utero.

UFH (unfractionated heparin) and low-molecular-weight-heparin (LMWH) exert their anticoagulant activity by activating antithrombin. UFH has activity against both factor Xa and thrombin, whereas LMWH has relatively little activity against thrombin. Heparins, UFH or LMWH are the preferred agents for anticoagulation in pregnancy. The main advantage of heparins over other anticoagulants is that there is no transplacental passage. Disadvantages of UFH include the necessity of parenteral administration, a 2% risk of major bleeding osteoporosis with a 17% to 36% reduction in bone density, a 2% risk of vertebral fracture and a risk of heparin-induced thrombocytopenia (HIT) *(9)*.

Over the last ten years LMWHs have become the preferred anticoagulants for treating and preventing thromboembolism in all patients. LMWHs are fragments of unfractionated heparin produced by an enzymatic or chemical depolymerization process with a mean molecular weight of approximately 5000 daltons. Compared with UFH, LMWHs have relatively greater activity against factor Xa and are less likely to bind to plasma proteins, endothelial cells and macrophages. This reduction in binding increases the bioavailability, half life and anticoagulant activity of LMWH relative to UFH. Although parenteral administration is still required, potential advantages of LMWHs over unfractionated heparin are less bleeding, less bone loss, a more predictable response, a lower risk of HIT, a longer half-life and demand less-intensive monitoring. Like UFH there is no transplacental passage. The physiologic changes of pregnancy alter the metabolism of LMWH, resulting in lower peak levels and a higher rate of clearance, and so pregnant women may need higher doses or more frequent dosing.

Fondaparinux, a selective inhibitor of factor Xa, is a pentasaccharide that mimics the active site of heparin that binds to antithrombin. Fondaparinux is administred subcutaneously. In in vitro models, there was no placental transfer. Fondaparinux may be the preferred alternative to heparins in the case of heparin allergy or HIT in pregnancy *(7)*.

Aspirin is an antiplatelet drug rather than an anticoagulant. Low dose aspirin (81 mg per day) has been extensively evaluated during pregnancy and has been shown to be safe and effective in reducing the risk of preeclampsia in high risk women, and in women with antiphospholipid antibodies and recurrent pregnancy loss. Large, randomised trials have demonstrated no increased risk of miscarriage, congenital anomalies, placental abruption, fetal haemorrhage or neonatal bleeding. In women with either mechanical heart valves or in antiphospholipid syndrome, low-dose aspirin may be used in combination with heparins *(10)*.

Women with history of myocardial infarction, with risk factors for arterial thrombosis and mechanical heart valves use other antiplatelet agents for supplemental therapy. There are no data for placental transfer of dipyridamole, clopidogrel and ticlopiridine.

Thrombolysis is indicated for life threatening thromboembolism. There are recent reports of its use in pregnancy to treat pulmonary embolism, coronary artery thrombosis, massive deep vein thrombosis, cerebral vein thrombosis and mechanical valve thrombosis. Thrombolytic agents such as urokinase, streptokinase and recombinant tissue plasminogen activator do not cross the placenta, but can potentially jeopardize the fetus if bleeding occurs in the retroplacental space. The risk of fetal loss has been estimated to be 5.8% and the risk of maternal mortality to be 1.2%.

Women of lifelong anticoagulation may be converted from warfarin to LMWH before pregnancy or as soon as possible after conception. Although the use of pneumatic compression devices for the prevention of peripartum thrombosis has not been studied, extrapolation from perioperative data would suggest benefit. The devices may be placed in labor after epidural administration or before caesarean delivery.

Guidelines have been developed for antithrombotic therapy during pregnancy. These recommendations are usually consensus, rather than evidence-based and involve assessing VTE risk. Heparin prophylaxis is recommended for those in higher-risk categories. As 50% of VTE occurs postpartum, these guidelines recommend heparin or warfarin for 6 weeks postpartum in women with history of VTE or thrombophilia. VTE during pregnancy is treated with therapeutic heparin.

Neuraxial anaesthesia

There is considerable debate about administering neuraxial anaesthesia in parturient with thrombocytopenia. A platelet count from 70×10^9/L to 100×10^9/L in otherwise healthy parturient should not contraindicate regional anaesthesia. Most American anaesthesiologist would insert an epidural in a healthy parturient with platelet count $\geq 80 \times 10^9$/L. The situation is more controversial in the setting of preeclampsia, including HELLP syndrome. In this situation, most anaesthesiologist considers the platelet count, the clinical picture and whether the thrombocytopenia is stable or decreasing.

Heparin therapy should be temporarily stopped during the immediate peripartum interval to minimise the risk of haemorrhage and to permit regional anaesthesia. Because of the theoretical risk of epidural spinal haemorrhage in women receiving heparin that undergo epidural or spinal anaesthesia many anaesthesiologist will not perform neuraxial regional anaesthesia in women who have recently received heparin. Since UFH has a relatively short duration of action, the American Society of Regional Anaesthesia states that subcutaneous UFH prophylaxis is not a contraindication to neuraxial regional anaesthesia. However, LMWHs should be stopped for at least 12 to 24 hours before regional anaesthesia can be considered safe *(11)*.

Anaesthesia guidelines advise waiting to insert the needle at least 10 to 12 hours after the last prophylactic dose of LMWH, and at least 24 hours after the last therapeutic dose. To facilitate use of regional anaesthesia in pregnant women on heparin, it's useful to electively stop LMWH 24 hours before planning induction of labour or electively stop prophylactic-dose LMWH or UFH at about 38 weeks of gestation to await spontaneous labour. Therefore, pragmatically is to switch therapeutic or prophylactic LMWH to UFH at about 36 weeks of gestation, with instructions to discontinue the injections in the earliest stages of spontaneous labour. This aims to shorten the heparin-free period required before neuraxial anaesthesia while minimizing maternal thrombotic risk.

Additional advantages to using UFH peripartum include the ability to completely reverse the heparin effect with

protamine sulphate if major bleeding occurs. LMWHs are only partially reversible.

Anaesthesiologists are commonly asked to provide epidural anaesthesia for labour and/or delivery in women using prophylactic heparin. There is justifiable concern about administering neuraxial anaesthesia in woman on heparin due to risk of a neuraxial haematoma. Neuraxial anaesthesia is contraindicated when a women is on therapeutic heparin. Consensus-based recommendations regarding neuraxial anaesthesia in patients on antithrombotics have been developed *(12)*.

Epidural spinal haemathoma are the most common type of spinal haemathoma, followed by subarachnoid haemathomas. Anticoagulants and antithrombotic drugs can increase the risk of spinal haemathoma formation, especially following neuraxial blockade. Neuraxial anaesthetic practice guidelines have been developed and revised to minimize the risk of spinal haemathoma in patients receiving LMWH as well as other newer anticoagulants *(13, 14)*.

CONCLUSION

Despite the increased risk of thrombosis in pregnancy, anticoagulants are not routinely indicated, because the risks usually outweigh the benefits. The exception is women on life-long anticoagulation or women with history of thrombosis or thrombophylia. Heparin therapy must be interrupted temporarily during the immediate peripartum interval to minimise the risk of haemorrhage and to allow for the option of regional anaesthesia.

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