ORIGINAL ARTICLE

A Review on Thromboprophylaxis in Pregnancy

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Summary

Thromboembolic disease remains an important cause of maternal mortality worldwide. The risk assessments for prevention of thromboembolism in pregnancy are controversial due to lack of large-scale randomised controlled trials. Unfractionated heparin is at present, the anticoagulant of choice during pregnancy. However, it may be superseded by low-molecular-weight heparin in the near future because of its safety and efficacy.

Key Words: Pregnancy, Thromboembolism prophylaxis, Warfarin, Heparin

Introduction

The incidence of venous thromboembolism (TE) has been estimated to be about 85/100,000 maternities[1]. Thromboembolic disease, albeit rare in pregnancy, has remained the greatest single cause of maternal mortality in developed countries[2-5] whilst all the other causes of maternal death have declined over the past 20 years. In Malaysia, pulmonary embolism has remained the third leading cause of maternal death since 1991[6]. The puerperium generally poses the greatest risk for TE but antenatal thromboembolic events appear to be on the increase.

Pathophysiology

Pregnancy is associated with five to six fold increased risk of TE[7]. This risk also extends into the puerperium. This may be explained by Virchow's triad of venous stasis, hypercoagulability and vascular wall injury as the major predisposing factors for thromboembolism[7] that is more common in pregnancy. Venous stasis in pregnancy may occur as a result of increased venous distensibility and capacitance from hormonal effect during pregnancy as well as mechanical obstruction on pelvic veins secondary to compression from the gravid uterus. The state of hypercoagulability in pregnancy is explained by the physiological increased levels of clotting factors (factors I, II, VII, VIII, IX, X) and decreased fibrinolysis in pregnancy. The former occurs by mid-pregnancy whereas the latter is greatest in the third trimester[8]. Pregnancy is also associated with alteration in levels of some of the important natural anticoagulants (antithrombin III, protein C, protein S and activated protein C (APC) cofactor); protein C and antithrombin III levels remain normal in pregnancy whereas protein S levels seem to decrease[7-8]. The exact role of APC resistance as a cause of TE during pregnancy although still unknown, has been implicated in a few recent studies[8-9]. Pilot studies have shown a general increase in APC resistance in pregnancy[9-10]. Factor

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V Leiden gene mutation with varied prevalence in different populations may also be another factor of increased TE risk[11-12].

Delivery itself is associated with vascular injury and an operative delivery may compound further changes at the utero-placental interface and hence explains the increased TE risk in the puerperium. Other important risk factors of TE in pregnancy include advanced maternal age (>35 years), multiparity, obesity, operative or difficult instrumental delivery, prolonged bed rest, pre-eclampsia, previous TE and thrombophilia[12-13] (Table I). One must bear in mind that multiple risk factors are often present in women with thromboembolic disease during pregnancy or puerperium and the risks are often cumulative.

Risk Assessment for Thromboprophylaxis in Pregnancy

The guidelines suggested in the report of the RCOG Working Party on thromboprophylaxis in pregnancy are summarised in Table II[13]. High risk patients would receive antenatal, intrapartum and postpartum thromboprophylaxis, whereas those considered as low risk would only receive intrapartum and postpartum anticoagulation[12,14]. A multicentre, prospective study that showed pregnant women with a single previous episode of venous TE but without evidence of thrombophilia to have low risk of recurrence of antepartum TE despite withholding antepartum thromboprophylaxis[15], this challenges the concept of routine antepartum thromboprophylaxis.

Table I
Summary of Risk Factors for Thromboembolism in Pregnancy and the Puerperium

Physiological Risk Factors	Anatomical Risk Factors	Other Risk Factors
* Increased levels of clotting factors I, II, VII, VIII, IX, X	* Pelvic veins compression from the gravid uterus	* Advanced maternal age (>35 years) * Obesity (> 80 Kg) * Multiparity (>4) * Prolonged bed rest (> 4 days)
* Increased natural Anticoagulant: protein S / ? increased APC resistance		* Major current illness (e.g. heart disease; nephrotic syndrome) * Operative or difficult instrumental delivery (vascular injury) * Excessive blood loss
* Decreased fibrinolysis		* Pre-eclampsia
* Increased venous distensibility & capacitance (hormonal effect)		* Previous thromboembolism or family history * Thrombophilia: - Inherited (Antithrombin III, Protein C, protein S deficiency, hyperhomocysinaemia, Prothrombin gene G20210A variant and APC resistance) - Acquired (Antiphospholipid syndrome)

Table II
Summary of RCOG Working Party Suggested Guidelines on Thromboprophylaxis in Pregnancy[13] and Arbitrary Classification of Risk Groups by other Authors[12,14] as Indicated by the Asterisk (*)

Risk Factors	Antenatal Thromboprophylaxis	Postpartum Thromboprophylaxis
• Previous venous TE (single event) in pregnancy with no other TE risk factors ***Low to moderate risk**	May be indicated	• - Graduated elastic compression stockings - Heparin/LMWH after normal delivery/ caesarean section Anticoagulation for minimum 6 weeks.
• Previous thrombosis outwith pregnancy - post surgery/injury or on contraceptive pills etc. ***Low risk**	Not indicated	• Only if patient underwent caesarean section
• Previous multiple thrombotic events ***High risk**	Start 4-6 weeks in advance of gestation at which the previous thrombosis occurred	• Minimum 6 weeks after delivery.
• Acquired thrombophilia (lupus anticoagulant/ anticardiolipin antibodies) ***Moderate risk**	Indicated in patients with previous clinical thrombotic event	• Advised minimum 6 weeks after delivery
• Inherited thrombophilia *Moderate risk	If other thrombophilic problems exist (e.g. pregnancy loss)	• Minimum 6 weeks after delivery
• With previous TE/family history of TE ***High risk**	Merits consideration	• Minimum 6 weeks after delivery
• Others (obesity, immobilisation, pre-eclampsia, major concurrent medical illness e.g. nephrotic syndrome) ***Moderate risk**	To be considered according to individual and level of risk	To be considered according to individual and level of risk (e.g. if caesarean section is required).
• Mechanical heart valve prosthesis ***High Risk**	Warfarin is at present generally preferred instead of heparin/LMWH	• Warfarin may be introduced 24 to 48 hours post delivery and heparin discontinued once optimal INR is achieved.

Patients who require obstetric thromboprophylaxis need to be assessed individually so that the type of anticoagulation and the duration of therapy can be determined. However, the safety and effectiveness of thromboprophylaxis in pregnancy remains controversial. Recommended practice guidelines on thromboprophylaxis produced by the Royal College of Obstetricians and Gynaecologists (RCOG)[13] are based only on expert opinion. The large-scale multicentre randomised controlled APPLE *(Assessment of the Prevention of Pulmonary embolism and deep venous thromboses using Low molecular weight Heparin)* and PEACH *(Prevention of pulmonary Emboli and deep venous thromboses After Caesarean section with low molecular weight Heparin)* studies, currently run by the Perinatal Trials Service will hopefully provide us with some information and sound basis for clinical practice in obstetric thromboprophylaxis.

Whilst awaiting the emergence of evidence-based practice guidelines on thromboprophylaxis in pregnancy, there are three main groups of patients in whom prophylaxis should be considered:-

1. those with risk factors for thromboembolism (e.g. obesity, age, parity, major medical illness or operative delivery)
2. those with previous history of thromboembolism in pregnancy or thrombophilia
3. those with cardiac disease (mechanical heart valve prosthesis, atrial fibrillation or enlarged left atrium require use of anticoagulants[16])

As thromboembolism risk is generally greatest in the puerperium[1,2,17], prophylaxis can be limited to the intrapartum and postpartum periods in the first group. Whereas those considered as high risk (Table II) would generally receive antenatal as well as intrapartum and postpartum anticoagulation. Anticoagulation is mandatory throughout pregnancy and the puerperium in the third group of women, especially in those with mechanical heart valves.

Prevention of Venous Thromboembolism

Common prophylactic measures for the prevention of venous thromboembolism include early ambulation post-operation, rehydration and the use of mechanical devices like elastic compressive stockings in the low-risk group. Other measures include the use of anticoagulants that interact with antithrombin III or antiplatelet agents like aspirin or Dextran that affect platelet function.

Choice of anticoagulation in thromboprophylaxis

Heparin and the coumarin derivative, warfarin are the two anticoagulants generally used in clinical practice. Heparin being the preferred choice is most commonly used for obstetric thromboprophylaxis because it does not cross the placenta. Warfarin, on the other hand, crosses the placenta and has adverse effects on the fetus throughout pregnancy. Therefore, during antenatal period, heparin or LMWH (low molecular weight heparin) is usually preferable to warfarin except in situation of mechanical heart valve prosthesis[13].

Heparin

Unfractionated heparin is available as a sodium or calcium salt; the sodium preparation is preferable for subcutaneous administration because it achieves higher plasma levels[7]. Commercial heparins are extracted from natural sources and are obtained from intestinal mucosa - mostly of pigs in Europe, South America, China or from bovine lung in the United States and Hungary[18]. With the recent problems of bovine spongiform encephalopathy (BSE), heparin crude material is presently obtained from porcine mucosa only[18]. In Malaysia, however, the unfractionated heparins used are generally of bovine origin. Most of the currently available LMWH is obtained from a chemical or enzymatic depolymerisation of the unfractionated heparin (UH) preparations extracted from porcine intestinal mucosa. The mean molecular weight of LMWH is only about one-third of that of unfractionated heparin[7]. The advantages of the low and homogenous molecular weight of LMWHs over UH include their high bioavailability of up to 90% as compared to 30% with UH and their predictable and sustained pharmaco-kinetics after subcutaneous administration[18]. As both UH and LMWH are eliminated primarily by the kidneys[19], the physiological increased renal clearance in pregnancy may therefore affect their pharmacokinetics[20] and hence the optimal dosing in pregnancy.

UH exerts its antithrombotic effect principally by combining with antithrombin III to form a complex with inhibitory action on factor Xa and thrombin (factor IIa)[12]. LMWHs, on the other hand, due to their predominant anti-Xa activities and minimal anti-IIa activities produce little bleeding complications for an equivalent antithrombotic effect when compared to UH.

UH although poses no risk to the fetus, is associated with a significant risk of maternal osteoporosis when used long-term[21]. This is particularly relevant as pregnancy itself and breast-feeding have independent effects on bone. Thrombocytopaenia is another well recognised complication of UH therapy with a reported incidence of 1 - 30%[10].

Thrombocytopaenia may be of early onset with mild symptomless presentation. However, the delayed onset, which occurs 6 to 10 days after treatment and is thought to be associated with a heparin-dependent IgG antibody, may be severe and is associated with a high incidence of thromboembolic complications. LMWHs offer several advantages over UH in that, the occurrence of these maternal adverse effects associated with UH is generally very rare with LMWHs[19,22]. With their favourable dosing regime and lack of need of routine monitoring as well as the safety and effectiveness, LMWHs may be replacing unfractionated heparin in TE treatment and prophylaxis in pregnancy in the near future.

Warfarin

Warfarin inactivates Vitamin K dependent clotting factors II, VII, IX and X. The dosing depends on the response of prothrombin time and more recently the International Normalised Ratio (INR). The one advantage of warfarin is that it can be taken orally but it has many disadvantages when used during pregnancy. It crosses the placenta and hence not only gives rise to fetal teratogenicity in the first trimester, but also increased bleeding tendencies in the fetus throughout pregnancy[10]. Other adverse effects include placental abruption and maternal haemorrhage. The adverse risks of warfarin thus outweigh its use in obstetric thromboprophylaxis except in cases of mechanical heart valve prosthesis.

Aspirin

Low-dose aspirin (60 - 150mg per day) preferentially inhibits the cyclo-oxygenase enzyme in the platelet and thus suppresses the production of platelet aggregation agent, thromboxane[10]. As platelet is unnucleated, the inhibition of platelet cyclo-oxygenase activity is irreversible for the whole of the platelet lifespan of 7 to 10 days.

The protective effect of low-dose aspirin against arterial and venous TE in non-obstetric patients is shown by a meta-analysis of trials on antiplatelet thromboprophylaxis from the Antiplatelet Trialists' Collaboration[23] and is further supported a large multicentre randomised Pulmonary Embolism Prevention (PEP) trial[24]. However, the question of whether aspirin is as effective as LMWH in preventing out-of-hospital venous TE remains unanswered. Although the maternal and fetal safety from the use of low-dose aspirin (60 - 75mg) in pregnant women have been established in the CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) trial[25], the use of aspirin in obstetric thromboembolism prophylaxis is yet to be established.

Dextran

Dextran is not an anticoagulant per se but it exerts its antithrombotic effects by modulating the coagulation system and via its plasma volume expansion effect, resulting in haemodilution and reduced blood viscosity. However, with the recent reports of acute fetal distress and anaphylactoid reaction associated with Dextran, its use in pregnancy is not recommended[13].

Mechanical Heart Valve

Thromboprophylaxis in pregnant women with mechanical heart valves is a separate entity. In the most comprehensive analysis thus far of anticoagulation of pregnant women with mechanical heart valves[26], when the three commonest anticoagulation regimes used were compared: oral warfarin alone; UH between 6 to 12 weeks of gestation followed by warfarin; and UH throughout the whole of pregnancy, thromboprophylaxis was found to be most effective with warfarin alone but the risk of warfarin embryopathy was 6%, with nasal

hypoplasia and epiphysis stippling being the commonest. Substituting UH between 6 and 12 weeks of gestation eliminated the fetopathic risk but was associated with an increased risk of maternal thromboembolic complications. The sole use of UH throughout pregnancy was, on the other hand, inadequate. The risk of valve thrombosis which carries an estimated 1% to 4% maternal mortality rate appeared to be lowest with the use of warfarin throughout pregnancy (4%) and increased with the use of heparin. The estimated risk of maternal haemorrhage usually associated with delivery was about 2.5% in pregnant women receiving anticoagulation[26]. LMWHs are evolving as an attractive option for prophylaxis in pregnant women with prosthetic heart valves because of their effective antithromboembolic actions with less bleeding complications. LMWHs may well be the optimal future management of these patients. However, as data on this is currently lacking[26] close discussions with the cardiologist and careful considerations by balancing the fetal and maternal risks is of paramount importance prior to the use of LMWHs for mechanical heart valve thromboembolism prophylaxis.

Regimes and Dosage of anticoagulant in pregnancy

Although the ideal thromboprophylaxis in the antenatal period remains controversial, it is generally agreed that any pregnant woman with a previous history of deep vein thrombosis should receive at least 6 weeks of postpartum thromboprophylaxis. As the conditions that precipitate thrombosis are usually initiated intrapartum, anticoagulant prophylaxis is generally started during delivery or before an operative delivery.

The optimal dosage or duration of unfractionated heparin or LMWH in antenatal thromboprophylaxis has yet to be established. Generally, subcutaneous UH in a dose of 7,500 - 10,000 12 hourly is employed[13]. Alternatively, a LMWH like enoxaparin (Clexane®, Rhône Poulenc Rorer, France) 40mg/day or dalteparin (Fragmin®, Pharmacia & Upjohn, Sweden) 5000IU/day may be used. In high-risk pregnant women (Table II), 10,000IU of UH twice daily or appropriate dosage of LMWH is recommended. In these cases, the dosage of heparin may be adjusted accordingly to the anti-factor Xa activity with the aim of a target level of 0.2 - 0.4IU/ml. A safe and effective dose for obstetric thromboprophylaxis in the range of 2500 - 22,000U for dalteparin, 20 to 80mg for enoxaparin and 2050 - 15,000U for nadroparin (Fraxiparin®, Sanofi -Synthelabo, France) has been suggested[27]. From the extensive experience on enoxaparin and dalteparin, these two preparations are currently the recommended choices of LMWHs in pregnancy[19]. Until further prospective randomised controlled trials on LMWHs and UH are performed to resolve the issue on optimal dosage in pregnancy, the general recommended dose of dalteparin and enoxaparin for venous thromboprophylaxis is 100U/kg in two divided doses and 0.5mg/kg 12 hourly respectively[19]. The twice daily dosing of LMWH is based on the drug half-life of 3 to 4 hours. In the puerperium, as physiological alteration in metabolism that occurs in pregnancy rapidly returns to normal, postpartum thromboprophylaxis generally consists of UH in a dose of 5000IU subcutaneously 12 hourly, or a single daily injection of LMWH such as enoxaparin 20mg/day or dalteparin 2,500IU/day[13]. Warfarin can be introduced 24 to 48 hours after delivery but heparin is continued until the INR of 2 to 2.5 is achieved. Postpartum prophylaxis is generally continued for a minimum of 6 weeks.

Monitoring of anticoagulant in thromboprophylaxis

Regular monthly platelet count should be monitored in women on long-term heparin (more than 5 days)[12]. There are conflicting opinions on the need of coagulation profile monitoring with prophylactic dose of UH[10,28]. As prophylactic dose of UH does not lower the concentration of coagulation factors, crude tests like the activated partial thromboplastin time (APTT)[10] and

thrombin time (TT) cannot be used to measure the low prophylactic dose of heparin in the plasma. The former, which is also highly reagent dependent, is used to monitor therapeutic doses of UH in venous TE whilst the latter is particularly sensitive to therapeutic levels of UH and hence useful in assessing overdose of UH. Measurement of low prophylactic levels of heparin in the plasma can be assessed by a more specific method based on the ability of heparin in the neutralisation of factor Xa[10]. In the case of LMWH, its use at fixed dosage in venous thromboprophylaxis and treatment without laboratory monitoring has been shown to be efficacious and safe[28-30]. This is also coupled with the fact that anti-Xa level is a poor predictor of bleeding risk and antithrombotic efficacy in thromboprophylaxis[29].

Overall, it has been readily accepted that prophylactic heparin therapy does not require laboratory monitoring in 99% of cases[28]. However, there is insufficient data in pregnant women and hence it is unclear if the same conclusion could be drawn on pregnant women on thromboprophylaxis. The APPLE and PEACH trials may hopefully be able to throw some light on this. Warfarin use on the other hand requires regular monitoring by INR and the dosage adjusted accordingly.

Regional anaesthesia in women on thromboprophylaxis

Although therapeutic heparin or warfarin is clear contraindication to the use of regional anaesthesia, the issue with prophylactic heparin is contentious. The risk of spinal haematoma with anticoagulants although present, is very low[31]. An extensive review on prophylactic and therapeutic LMWH and regional anaesthesia has recommended against catheter placement within 10 to 12 hours of the last dose of LMWH. In addition, LMWH should be restarted for at least 6 to 8 hours after catheter removal[32]. This recommendation is generally also applicable in cases of UH thromboprophylaxis.

Guidelines for the management of labour and operative delivery in woman on thromboprophylaxis

For women receiving some form of antenatal prophylaxis, Letsky[10] has recommended the general management of these women going into labour as followed:-

* UH: reduce from 10,000 to 7,500IU subcutaneous 12 hourly; LMWH: continue with 40mg enoxaparin daily or dalteparin 5000U daily. Continue with heparin/LMWH throughout labour and /or operative delivery.
* In the event of an overdose of subcutaneous UH, careful repeated dosage of protamine sulphate (1mg per 100 U heparin intravenously over 10 minute with a maximum of 50mg) is needed as excess protamine sulphate can also act as an anticoagulant. Fresh frozen plasma (FFP) is not useful in these cases, as the circulating heparin will prevent the generation of thrombin[10].
* Haemorrhagic hazard has not been reported to date when LMWH is used in the conventional prophylactic dose. However, depending on the specific LMWH used, protamine sulphate will neutralise the haemorrhagic effect of LMWH overdose less efficiently when compared to UH.
* The decision to use regional anaesthesia should be made on an individual basis. Intrapartum therapy is not an absolute contraindication for regional anaesthesia. However, the general recommendation is that placement of epidural catheter or spinal anaesthetic should be avoided for at least 4 hours after the last subcutaneous administration[10]. Some authorities feel that regional anaesthesia is not contraindicated if the APTT (activated partial-thromboplastin time) is normal and heparin has not been administered within 4 to 6 hours of the procedure[7,13].

In women with mechanical heart valves, intravenous heparin may be prescribed. However, if the woman goes into labour or requires urgent delivery[10]: -

* It is usually sufficient to stop the intravenous heparin as the heparin activity will have fallen to safe levels within an hour.
* Protamine sulphate may be used as above if more urgency is demanded.

In a rare event when a woman goes into labour fully warfarinised as may occur in those with mechanical heart valves, the recommendations are[10]:-

* Give FFP (fresh frozen plasma) rapidly to correct the prothrombin time to normal.
* The infant should be delivered by the least traumatic method and screened for internal haemorrhage. Intravenous vitamin K and FFP should also be administered.

In all these cases, heparin should be continued post delivery and warfarin can be introduced 24 to 48 hours post-delivery whilst continuing with heparin until the INR is 2.0 - 2.5. The women should be advised that there is no contraindication to breast-feeding with the use of these anticoagulants postnatally.

Conclusions

Thromboembolic events remain the most common cause of maternal death. As yet, there are very few randomised clinical trials on obstetric thromboprophylaxis to guide clinicians in making decision on treatment and prevention of TE. Heparin is generally preferred to warfarin as the anticoagulant of choice in obstetric thromboprophylaxis. At present, at least in Malaysia, the use of UH supersedes that of LMWH due to the high cost of the latter and also on religious ground due to the porcine preparation of LMWH. Although low-dose UH has prophylactic effect, its long-term administration may be associated with adverse effects like osteopaenia and thrombocytopaenia. In developed countries, LMWH is increasingly the preferred choice in pregnancy because of its favourable pharmacokinetics, dosing regimen, lack of need for routine monitoring as well as its safety and efficacy in thromboprophylaxis. However, until more data is available from randomised controlled multicentre studies on the general use of LMWH in obstetric thromboprophylaxis, the optimal regime has yet to be determined.

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