

Review Article

Low molecular weight heparin: a promising anticoagulant in pregnancy

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ABSTRACT

Venous thromboembolism (VTE) is a leading cause of maternal mortality and morbidity during pregnancy in developed countries. The incidence of VTE increases about 4-fold during pregnancy and at least 14-fold during the puerperium. Risk factors include a personal history of VTE, presence of inherited or acquired thrombophilia, a family history of VTE and general medical conditions, such as immobilisation, overweight, varicose veins, some haematological diseases and inflammatory disorders. VTE is considered potentially preventable with the prophylactic administration of anticoagulants. Low molecular weight heparin has emerged as choice of anticoagulant in the present day obstetric and infertility practice. It has many advantages over unfractionated heparin and warfarin. Longer duration of action, less frequent dosing schedule, better safety profile are few of the advantages. Higher cost as compared to warfarin and unfractionated heparin is the main limiting factor for its use.

Keywords: Low molecular weight heparin, Anticoagulants in pregnancy, Venous thromboembolism, Heparin induced thrombocytopenia

INTRODUCTION

Venous thromboembolism (VTE) is an important cause of maternal mortality and morbidity during pregnancy and puerperium.¹ The incidence of VTE increases about 4-fold during pregnancy and at least 14-fold during the puerperium.² Risk factors include a personal history of VTE, presence of inherited or acquired thrombophilia, a family history of VTE and general medical conditions, such as immobilisation, overweight, varicose veins, some haematological diseases and inflammatory disorders.^{3,4}

The increased risk of venous thromboembolism during pregnancy is due to physiologic, mechanical and, sometimes, iatrogenic factors. Gravida have greater concentrations of factors I, VII, VIII, IX, and X; decreased fibrinolytic activity; and increased platelet activation. These changes in the coagulation system predispose the gravida to clot formation.⁵ The enlarging

uterus can compress venous drainage from the lower extremities, resulting in stasis. Further, prolonged immobilization in the form of bed rest is often prescribed for obstetric complications such as hypertension, preterm labor, haemorrhage, and preterm premature rupture of membranes. Both abdominal and vaginal operative delivery can predispose to vascular endothelial injury. VTE is considered potentially preventable with the prophylactic administration of anticoagulants, but there are no high quality randomized clinical trials that compared different strategies of thrombo-prophylaxis in pregnant women.⁶⁻⁸ Anticoagulant treatment is advocated in several situations during pregnancy. Venous thromboembolism disease, valvular or congenital heart disease, heart rhythm disorders or risk of thrombosis due to inherited or acquired thrombophilias. In recent times, thrombo-prophylaxis is advocated in women with poor obstetric history or with recurrent pregnancy loss or repeated failed attempts of in vitro fertilization.¹⁻⁵

AVAILABLE OPTIONS FOR ANTICOAGULATION DURING PREGNANCY

Warfarin

Although it is the drug of choice in the non-pregnant population, warfarin is contraindicated in pregnancy because it can cross the placenta and has been linked to adverse pregnancy outcomes. Several studies have demonstrated an association between first-trimester warfarin exposure and a constellation of structural birth defects, termed “Warfarin embryopathy”, which includes craniofacial and skeletal defects.⁹

Heparin

Heparin is the sole choice for long-term anticoagulation, since warfarin is contraindicated in pregnancy. Unfortunately, heparin has disadvantages that render it a second-line agent in the non-pregnant population. Because of enzymatic degradation, heparins cannot be given orally. In addition, because of its large size and strongly positive charge, the parent heparin molecule - known as “un-fractionated” heparin - is rapidly deactivated by tissue proteins, making for an unpredictable anticoagulation response. Under dosing and overdosing are typical and frequent monitoring is necessary. Heparin have found to be useful in antiphospholipid antibody syndrome.¹⁰

Low molecular weight heparin (LMWH)

Low molecular weight heparin is safe for both mother and fetus. It is as effective in pregnancy as in the non-gravid population, and side effects are minimal. It also has a favourable dosing route and interval, with less need for monitoring than with Un-fractionated Heparin (UH). Both the American college of obstetricians and gynaecologists and the society for maternal-fetal medicine endorse its use in pregnancy with appropriate counselling.¹¹⁻¹² This agent is produced by the controlled enzymatic degradation of un-fractionated heparin (molecular weight of approximately 10000 to 15000 daltons) into approximately 5000-dalton molecules. Although they are much smaller than the parent molecule, these polymers still carry a strong positive charge.

HOW DOES LMWH DIFFERENT FROM UN-FRACTIONATED HEPARIN?

LMWH is more efficient. Both UH and LMWH contain an essential pentasaccharide within their polymer structure that binds to and enhances anti-thrombin III, which in turn inhibits thrombin and activated factor X (Xa). Because of its smaller size, LMWH preferentially inhibits Xa, which is higher in the coagulation cascade. Inhibition of a single molecule of Xa prevents the formation of many molecules of thrombin. LMWH has

longer-lasting effects and subcutaneous dosing. It also has fewer side effects than UH.¹³

ADVANTAGES OF LMWH

Because of its smaller size, LMWH is rapidly and predictably absorbed from a subcutaneous injection. Intravenous dosing is not necessary to obtain adequate tissue levels. Once in tissue, it is deactivated more slowly and therefore maintains its anticoagulation effect longer. A longer half-life also translates to more favourable dosing routes (subcutaneous rather than IV) and regimens (daily versus twice daily). Similarly, since the dose-response is predictable and tissue levels are more constant, frequent monitoring of treatment response is not routinely necessary. Patients on LMWH have decreased risk of haemorrhage, osteoporosis, and anti-body-mediated thrombocytopenia.¹⁴

ADVANTAGES AND DISADVANTAGES OF LMWH IN PREGNANCY

Advantages

More effective anticoagulation, better dose-response, longer half-life, decreased need for monitoring, fewer side effects.

Disadvantages

Longer half-life, Risk of hematoma with epidural anaesthesia, not fully reversible with protamine sulfate, Anticoagulation effect difficult to monitor, higher cost.

MECHANISM OF ACTION

Both UH and LMWH mainly act by inactivating the factor Xa through the binding of antithrombin III and its subsequent activation.

REVIEW OF LITERATURE

Use of Low molecular weight heparin from first trimester of pregnancy - a retrospective study of 111 consecutive pregnancies by Philippe Derulie et al. N=97 (111 pregnancies) Patients with very high risk for thrombosis. Conclusion: The use of LMWH prescribed from the first trimester of pregnancy appears to be safe for mother and fetus. LMWH may be used as a first-line treatment from the first trimester of pregnancy, when necessary.¹⁵

Heparin treatment in pregnancy loss: Potential therapeutic benefits beyond anticoagulation, study by Gullermina Gilardi. In addition to direct effects of heparin on the coagulation cascade, heparins (UFH & LMWH) might protect pregnancies by reducing the binding of anti-phospholipid antibodies, reducing inflammation, facilitating implantation and or inhibiting complement activation.¹⁶

Nimes obstetricians and hematologists - Abruptio placentae (NOH-AP) trial pilot, randomized, controlled study (N=16), inclusion criteria - previous abruptio placentae (no foetal loss and -ve for antiphospholipid antibodies), treatment arms - enoxaparin (n=80)/No enoxaparin (n=80), primary outcome - composite of at least one of the following: Abruptio placentae, Preeclampsia, Birthweight <5th percentile, foetal loss after 20 weeks. Results: Enoxaparin was associated with a lower frequency of primary outcome [12.5% (10/80) vs. 31.3% (25/80)], There were no obvious side-effect, no thrombocytopenia, No major bleeding event. Conclusion: Enoxaparin given early during the second pregnancy decreases the occurrence of placental vascular complications in women with a previous placental abruption during their first pregnancy.¹⁷

Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin, N=50 (61 gestations), Inclusion criteria- Recurrent pregnancy loss (RPL) [≥ 3 losses in 1st, ≥ 2 losses in 2nd and ≥ 1 loss in 3rd trimester] with thrombophilia. Interventions - enoxaparin 40 mg/day in women with solitary thrombophilic defect, enoxaparin 80 mg/day in women with combined thrombophilic defects. Treatment administered throughout gestation until 4 weeks after delivery. Results: 46/61 (75%) gestations treated by enoxaparin resulted in live birth compared to only 38/193 (20%) of the untreated pregnancies (P <0.00001). In 23 women without a single living child following 82 untreated gestations, antithrombotic therapy resulted in 26/31 (84%) successful deliveries (P <0.0001). In 20 women with a prior living child, antithrombotic therapy improved successful delivery from 33/86 (38%) to 20/21 (95%) (P <0.0001). Conclusion: Enoxaparin is safe and effective in prevention of pregnancy loss in women with inherited and acquired thrombophilia.¹⁸

In a study in 3 women with high factor XI and recurrent pregnancy loss (19 previous pregnancy losses and 0 live births), enoxaparin administration in 5 subsequent pregnancies lead to 6 term live births and 1 miscarriage.¹⁹

In a study in Japanese women, there was no increase in hemorrhagic complications and less prolongation of activated partial thromboplastin time with thromboprophylaxis using LMWH compared to UFH soon after cesarean section.²⁰

Enoxaparin versus fractionated heparin in recurrent abortion secondary to antiphospholipid syndrome. Conclusion: LMWH plus low dose aspirin (LDA) was successfully used as an alternative to UFH plus LDA in the management of recurrent abortion secondary to Anti-Phospholipid Syndrome (APS). The results highlight the need for a larger randomized controlled trial to determine whether LMWH plus LDA should be the treatment of choice for recurrent abortion secondary to APS.²¹

Low-molecular-weight heparin or warfarin for anticoagulation in pregnant women with mechanical heart valves: what are the risks? A retrospective observational study. Unfractionated heparin has been shown to result in unacceptably high maternal morbidity. Low-Molecular-Weight Heparin (LMWH), used with or without aspirin (75-100 mg), has been increasingly used as the anticoagulant of choice in pregnant women.²²

Successful pregnancy outcome in women with bad obstetric history and recurrent fetal loss due to thrombophilia: effect of unfractionated heparin and low-molecular weight heparin. There was a complete resolution of thrombus in all the cases. None of the patients had any adverse reactions such as heparin-induced thrombocytopenia, thrombosis, or fracture. Both unfractionated heparin and low-molecular weight heparin were effective in cases of bad obstetric history and recurrent pregnancy loss due to thrombophilia. However, low-molecular weight heparin was found to be more effective than unfractionated heparin along with other advantages of not requiring laboratory monitoring and easy administration. None of the patients in either group had to interrupt the therapy for any adverse treatment-related complications.²³

Use of low molecular-weight heparin from the first trimester of pregnancy: a retrospective study of 111 consecutive pregnancies by Philippe Deruelle revealed that use of LMWH in first trimester of pregnancy appears to be safe for fetus and mother.²⁴

CONCLUSION

Low Molecular Weight Heparin (LMWH) is a new promising anticoagulant available for use during pregnancy. Safety of this drug has been proved in second and third trimester. It has a better safety profile with low incidence of heparin induced thrombocytopenia and osteoporosis. It has longer half-life, thus require less frequent injections. It has reliable pharmacokinetics thus less monitoring is required. The risk of maternal and fetal bleeding is less. It has longer anti Xa factor activity. The drug has emerged to be the favourite of obstetrician and infertility specialist due to its above mentioned advantages.

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