EDITORIAL

Low Molecular Weight Heparin in Obstetrics

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"Thrombosis in the Vessels is Nobody's Disease and Everybody's Complication"

Heparin was the first anticoagulant agent to be discovered and isolated for medical use in 1916 while working on the presumed functions of liver extracts. From 1971 onward, it was in regular use for the prevention of postoperative thrombotic events. Johnson during his research work on anticoagulants in 1976 found that the use of heparins with different molecular weights showed higher bioactivity with lower molecular weights in terms of higher values of antifactor [activated factor X (Xa)]. This pathbreaking finding revolutionized and thus began the discovery of the following one of the most important groups of drugs: Low molecular weight heparins (LMWHs).[1]

Heparin is an assorted mix of polysaccharide chains ranging in molecular weight from 3000 to 30,000. Also, LMWHs are made from unfractionated heparin (UFH) by splitting it into roughly one-third of the original size. Furthermore, LMWHs are glycosaminoglycans, consisting of chains of D-glucosamines and glucuronic acid or iduronic acid, with a rough molecular weight of 5000. The different LMWHs available in the market are enoxaparin, dalteparin, nadroparin, parnaparin, and tinzaparin. Different LMWHs not only differ in their molecular weights but also in bioactivity, pharmacodynamics, pharmacokinetics, recommended doses, and efficacy/safety ratio.[1–3]

Mechanism of Action

The LMWHs form a complex with thrombin resulting in the inhibition of Xa. It also has anti-IIa action. As LMWH's are small chain molecules they cause less inhibition of thrombin *via* the antithrombin route. So, what they lose in their strength being a small chain, they compensate with increased bioavailability and prolonged half-life. The effectiveness of LMWHs is further exaggerated by their resistance to inactivation by platelet factor 4 and by want of protein binding.

They also reduce inflammation, inhibit complement activation, reduce trophoblast apoptosis, and increase proteases involved in the trophoblast invasion of the maternal decidua in pregnancy.[2,3]

Pharmacokinetics

The LMWHs have poor binding with plasma proteins (<10%) ensuring higher bioavailability and predictable action, they also do not bind to endothelium or macrophages, thus avoiding the rapid uptake as in the case of UFH. The metabolism is by desulfation and depolymerization and excretion is by the renal system. The elimination is dose-independent.

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When used at thromboprophylactic doses, the transplacental passage is unknown making it safe for the fetus.

Monitoring of LMWH activity, remains the most debated area, sparking many arguments. Anti-Xa levels are not a good predictor of bleeding and antithrombotic efficacy in thromboprophylaxis, as indicated by the literature. Due to the reason that LMWHs have reliable pharmacokinetics and hemodynamics, hemostatic changes in pregnancy are well known; thus, the need for LMWH can be foreseen. So, is there a need to monitor?[2,4,5]

Uses in Obstetrics

Thrombophilia-related Complications

Anticoagulants during pregnancy are used for the following indications: Treatment of Venous thromboembolism and thromboprophylaxis. In the acute scenario of VTE, LMWH is to be used in standard doses, as per the total body weight—if the VTE has occurred during pregnancy one should be using the early pregnancy weight or the present weight if it occurs during the puerperium. Due to increased rate of clearance of LMWH in pregnancy, dosing should be made twice daily. I suggest continuing the therapeutic dose of LMWH for 1 month before changing to a prophylactic dose, taking into account the presence of risk factors underlying thrombophilia, obesity, operative procedures, and ambulation of the patient.

Pregnancy is a hypercoagulable state with an increased incidence of VTE due to multiple mechanisms. Thus, identifying women with high risk factors is the mainstay to reduce VTE in pregnancy and improve feto–maternal outcomes. The risk factors are body mass index (BMI) above 35, Gestational diabetes, autoimmune disorders, antiphospholipid (APLA) syndrome, preterm birth, preeclampsia, assisted reproductive technology, cesarean delivery with associated mobility problems, stillbirths, obstetric hemorrhage, postpartum infection. These risk factors should be

documented and the risk score should be assessed for starting the thromboprophylaxis.

Autoimmune Disorders

First trimester pregnancy failure is a predominant presentation of primary APLA or secondary APLA in other autoimmune disorders such as systemic lupus erythematosus (SLE). It accounts for about 20% of all the recurrent miscarriage. It is proved it interferes with the trophoblastic invasion and also cause microthrombi in the placental vessels. Various regimens have been proposed and suggested for treating APLA syndrome, using aspirin, prednisone, UFH, and LMWH. Furthermore, LMWH is used as a valuable tool to prevent the recurrence of miscarriage in such patients. The use of LMWH in these patients is in a standard dosage of 40-mg once daily of enoxaparin or equivalent, however, a higher dose may be safely used in women with a high thrombotic risk score.

Placenta Mediated Pregnancy Complications [Recurrent Pregnancy Loss, Fetal Growth Restriction (FGR), Preeclampsia, Abruptio Placentas, and Intrauterine Fetal Demise]

Although the precise pathogenesis of Preeclampsia, abruptio placentae, FGR, and intrauterine fetal death is still unclear, these obstetric complications have been associated with abnormal development of placental vasculature and hemostatic disturbances: the most common placental findings seen in these cases are multiple placental infarcts, thrombosis of fetal vessels, thrombosis of spiral arteries, and fibrin deposition around the developing villi—commonly labeled as abnormal placentation or placental dysfunction. The high frequency of thrombophilic mutations in women with these complications indicates the likely involvement of the hemostatic system.

The link between placenta-mediated pregnancy adverse effects and inherited/acquired thrombophilias and the improved outcome with antithrombotic therapy in APLA syndrome with recurrent spontaneous abortions (RSA) led to the use of LMWH for such conditions. LMWH has proved its benefit in the treatment of these women in succeeding pregnancies in terms of live birth, onset of preeclampsia, improved birth weight, and abruptio placentae. The positive LMWH effect on feto–maternal circulation in these women can be seen as better uterine artery Doppler indices.

The LMWH directly promotes trophoblast cell invasiveness by acting on endometrial proteases and prevents trophoblastic apoptosis. It also has anti-inflammatory properties by preventing complement activation and reducing cytokines and vascular adhesion molecules concentration. Also, LMWH reduced the recurrence of adverse obstetric results.

Advantages

The LMWH is used as subcutaneous s in a fixed dose and gives a predictable response in terms of anticoagulation, thus preventing the need for monitoring. The injection can be self-administered by the patient at home. Moreover, LMWH is used as precise dosing.

Adverse Effects

Placental transfer and teratogenicity: No transplacental transfer and no teratogenicity were noted. The predictable risk of hemorrhage with LMWH is minimal and one should remember that protamine does not reverses the action of LMWH.

Eventually, LMWH is one molecule which has changed the practice of the obstetrics, but like all good things, it has to used or abused is to be decided by the clinician.

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