Use of Low Molecular Weight Heparin in Obstetrics

Dr Rajendra Sankpal
MD, DNB, FCPS, DGO, DFP, MB, Diploma Advanced Laparoscopy (USA)
Consultant Gynecologist
Holy Spirit Hospital
Dr L H Hiranandani Hospital, Mumbai

Introduction

The indications to the use of heparin, in particular low-molecular-weight heparin (LMWH), during pregnancy have been extensively studied in preventing not only thromboembolic disease but also pregnancy complications associated with thrombophilia. These complications include recurrent pregnancy loss (RPL), fetal growth restriction (FGR), preeclampsia (PE), abruptio placentae, and intrauterine fetal death (IUFD). It is well accepted that LMWH may offer clinical advantages over unfractionated heparin (UFH), including longer duration of action, more predictable response, and once-daily subcutaneous administration. LMWH might protect pregnancy by reducing inflammation, inhibiting complement activation, and favoring implantation.

Thrombophilia and Pregnancy Complications

Thrombophilic disorders affect at least 15% of Western population. Thrombotic events of placental vessels may be involved in serious obstetric complications by impairment of placental perfusion. The placental perfusion may be compromised by disturbances of hemostasis leading to a prothrombotic state, maternal acquired or congenital thrombophilias are suggested to be involved in RPL, intrauterine fetal loss, FGR, and PE. The most commonly inherited thrombophilias are Factor V Leiden (FVL) gene mutation, prothrombin gene mutation (FII 20210A), hyperhomocysteinemia, and natural anticoagulant deficiencies including antithrombin (AT), protein C (PC), and protein S (PS).

Furthermore, the acquired thrombophilic disorder is the antiphospholipid syndrome (APS), which is diagnosed when thrombosis or pregnancy morbidity occurs in persistently antiphospholipid antibodies (aPL)-positive individuals.ery 2 months

Low-Molecular-Weight Heparin Use in Patients With Thrombophilic Disorders

Although the pathogenesis of pre eclampsia, abruptio placentae, intrauterine growth restriction (IUGR), and intrauterine fetal death remains still unknown, these obstetric complications have been associated with abnormal placental vasculature and hemostatic disturbances. The most prominent placental lesions are multiple infarcts, thrombosis of fetal stem vessels, spiral artery thrombosis.[1] The high prevalence of thrombophilic mutations in women with PE, IUGR, and abruptio placentae have suggested the possible involvement of hemostatic system in these complications.[1] However while the antithrombotic prophylaxis is accepted throughout pregnancy and postpartum periods to women with thromboembolic events before and/or during pregnancy, there is still controversy as to whether this treatment can reduce their recurrence in patients with thrombophilias and previous obstetric complications.

Antiphospholipid syndrome is one of the few treatable causes of pregnancy loss and successful pregnancy rates of more than 70% can be achieved with appropriate treatment.[2] Different regimens have been proposed for treating APS, including aspirin, prednisone and aspirin, and heparin and aspirin. The current recommendation is to use low-dose aspirin (LDA) and prophylactic or therapeutic doses of heparin for patients fulfilling the Updated Sapporo APS Classification Criteria.[3] and no

treatment for asymptomatic (no history of pregnancy and thrombosis) persistently aPL-positive patients.[4]

The association between placenta-mediated pregnancy complications and inherited/acquired thrombophilias and the improvement with antithrombotic therapy in APS with RPL has led to renewed interest in the use of LMWH for such pregnancy complications.[5] Patients with previous pregnancy complications - including RPL, PE, IUGR, IUFD, abruptio placentae - and thrombophilias could benefit from treatment with LMWH in subsequent pregnancies in terms of live birth, PE onset, abruptio placentae, and birth weight <5th percentile rate.[6-10] The positive LMWH effect on feto-maternal circulatory system in these patients was confirmed by the improved uterine artery Doppler flow indices.[11] It was observed that pregnancy outcomes were similar whether 40 mg or 80 mg regimens were used and that enoxaparin 80 mg neither increased bleeding complications nor heparin induced thrombocytopenia compared with 40 mg. The lower dosage of enoxaparin might suffice for thrombophilic women with standard risk, while a higher dosage might be beneficial and equally safe in women with a particularly high thrombotic risk.

LWMH, dalteparin, has been shown to have a similar role in preventing pregnancy complications. In particular, dalteparin, in combination with ASA, administered to women with inherited thrombophilia and previous pregnancy complications, significantly decreased the risk of PE by 20% and FGR by 30%[12] Presumably dalteparin might ultimately be proven to be effective in reducing placenta-mediated adverse pregnancy outcomes, despite not reducing systemic markers of coagulation activation and fibrinolysis. LMWH may have more than anticoagulant effects with respect to prevention of placenta-mediated pregnancy complications, as shown through the mice experiment where LMWH was able to reduce complement activation[13]

Low-Molecular-Weight Heparins' Efficacy in Patients Without Known Thrombophilias and With Previous Pregnancy Complications

Limited data are available regarding the antithrombotic prophylaxis with LMWH in women without thrombophilias at risk for recurrence of disease. Concerning RPL, this obstetric event continues to recur in 20% to 30% of cases.[43] According to The American College of Obstetricians and Gynecologists (ACOG) 2001, the use of empirical therapy in women with unexplained RPL is unnecessary in view of the fact that supportive care alone offers a chance of up to 75% for a successful pregnancy.[14]

The LMWH inefficacy in reducing the recurrence of pregnancy loss might be attributable to the concept that RPL is due to other causes than thrombosis and to the interindividual efficacy of this treatment. According to recent reports, women with PE appear to have higher systemic inflammatory response than women with normal pregnancy.[17,18] During the first and second trimester, the risk for PE has been correlated with increased serum levels of many inflammatory markers as TNFα, IL-2, vascular adhesion molecules, and activation of leukocytes.[18] The potential benefit of heparin in these cases could be related to its anti-inflammatory.[15,16] Mello et al indicated that in women with a previous history of PE, without thrombophilic factors, LMWH reduced the recurrence of adverse clinical outcomes.[18]

In a recent randomized controlled study, Rey et al [19] evaluated the role of dalteparin versus no treatment in patients with previous pregnancy complications without thrombophilias. They observed a significant decreased rate in placental-mediated complications using prophylactic doses of dalteparin administered before 16 weeks of gestation. Such reduction was from 23.6% to 5.5% with a relative risk reduction of 76.7%.

Safety Profile of LMWH

Adverse fetal outcomes were recorded if fetal or neonatal death occurred or if congenital malformations were present. The observed rates reported were of almost 3.26% similar to the

incidence observed in pregnant women treated with UFH (unfractionated Heparin). All these incidences are close to those reported for the general population of pregnant women in both Europe and the United States.[21]

Long-term administration of LWWH during pregnancy has been associated also to maternal complications. The most relevant are bleeding complication, heparin-induced immune reactions, and finally osteoporosis. Regarding the last one side effect, evidence from animal studies indicated that LMWH might have a lower osteopenic effect than UFH. The collected data suggest a lower risk of heparin-induced osteoporosis with LMWH.[22]

Conclusions

Altogether the reported studies demonstrate a large heterogeneity of results about the role of LMWHs during pregnancy. Although treatment with LMWH appears promising with a reduction in PE, IUGR, and fetal loss recurrence, to date the numbers of studies and the relative participants are too small. Thus, it is difficult to establish a definitive conclusion because several important aspects should be considered in each study.

References

1. Nelson SM, Greer IA. The potential role of heparin in assisted conception. Hum Reprod Update. 2008;14(6):623–645. Abstract/FREE Full Text
2. Brenner B, Hoffmann R, Blumenfeld Z, Weiner Z, Younis JS. Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin. Thromb Haemost. 2000;83(5):693–697. MedlineOrder article via InfotrieveWeb of Science
3. Kupferminc MJ, Fait G, Many A, et al. Low molecular weight heparin for the prevention of obstetric complications in women with thrombophilias. Hypert Pregnancy. 2001;20(1):35–44.
4. Carp H, Dolitzky M, Inbal A. Thromboprophylaxis improves the live birth rate in women with consecutive recurrent miscarriages and hereditary thrombophilia. J Thromb Haemost. 2002;1(3):433–438. Web of Science
5. Gris JC, Mares P. The long and winding road…towards LMWH for pregnancy loss. J Thromb Haemost. 2005;3(4):224–226. CrossRefMedlineOrder article via InfotrieveWeb of Science
6. Gris JC, Mercier E, Querè I, et al. Low-molecular weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. Blood. 2004;103(10):3695–3699. Abstract/FREE Full Text
7. Grandone E, Brancaccio V, Colaizzo D, et al. Preventig adverse obstetric outcomes in women weith genetic thrombophilia. Fertil Steril. 2002;78(2):371–375. CrossRefMedlineOrder article via InfotrieveWeb of Science
8. Bar J, Mashiah R, Cohen-Sacher B, et al. Effect of thromboprophylaxis on uterine and fetal circulation in pregnant women with a history of pregnancy complications. Thromb Res. 2001;101(4):235–241. CrossRefMedlineOrder article via InfotrieveWeb of Science
9. Brenner B, Hoffmann R, Carp H, et al. Efficacy and safety of two doses of enoxaparin in women with thrombophilia and recurrent pregnancy loss: the LIVE-ENOX study. J Thromb Haemost. 2005;3(2):227–229. CrossRefMedlineOrder article via InfotrieveWeb of Science
10. Lindqvist PG, Merlo J. Low molecular weight heparin for repeated pregnancy loss: is it based on solid evidence? Thromb Haemost. 2005;3(2):221–223. CrossRef
11. Leduc L, Dubois E, Takser L, Rey E, David M. Dalteparin and low-dose aspirin in the prevention of adverse obstetric outcomes in women with inherited thrombophilia. J Obstet Gynaecol Can. 2007;29(10):787–793. MedlineOrder article via Infotrieve
12. Mousa HA, Alfirević Z. Thrombophilia and adverse pregnancy outcome. Croat Med J. 2001;42(2):135–145. MedlineOrder article via InfotrieveWeb of Science
13. ACOG. Management of recurrent pregnancy loss. Practice Bull. 2001;24(2):1–12.
14. Bose P, Black S, Kadyrov M, et al. Heparin and aspirin attenuate placental apoptosis in vitro: implications for early pregnancy failure. Am J Obstet Gynecol. 2005;192(1):23–30. CrossRefMedlineOrder article via InfotrieveWeb of Science

15. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science. 2005;308(5728):1592–1594. Abstract/FREE Full Text

16. Mello G, Parretti E, Fatini C, et al. Low-molecular weight heparin lowers the recurrence rate of preeclampsia and restores the physiological vascular changes in angiotensin-converting enzyme DD women. Hypertension. 2005;45(1):86–91. Abstract/FREE Full Text

17. Leach RE, Romero R, Kim YM, et al. Pre-eclampsia and expression of heparin-binding EGF-like growth factor. Lancet. 2002;360(9341):1215–1219. CrossRefMedlineOrder article via InfotrieveWeb of Science

18. Leach RE, Kilburn BA, Petkova A, Romero R, Armant DR. Diminished survival of human cytotrophoblast cells exposed to hypoxia/reoxygenation injury and associated reduction of heparin-binding epidermal growth factor-like growth factor. Am J Obstet Gynecol. 2008;198(4):471.e1–e7. CrossRefMedlineOrder article via Infotrieve

19. Rey E, Garneau P, David M, et al. Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women without thrombophila: a pilot randomized controlled trial. J Thromb Haemost. 2009;7(1):58–64. CrossRefMedlineOrder article via InfotrieveWeb of Science

20. Kher A, Bauersachs R, Nielsen JD. The management of thrombosis in pregnancy: role of low molecular weight heparin. Thromb Haemost. 2007;97(4):505–513. MedlineOrder article via InfotrieveWeb of Science

21. Lekfou E, Khamashta M, Hampson G, Hunt BJ. Low molecular weight heparin induced osteoporosis and osteoporotic fractures: a myth or existing entity? Lupus. 2010;19(1):3–12. Abstract/FREE Full Text

22. Janiaux E, Farquarson RG, Christinasen OB, Exalto N. Evidence-based guidelines for the investigation and medical treatment of recurrent miscarriage. Hum Reprod. 2006;21(9):2216–2222. Abstract/FREE Full Text