ORIGINAL ARTICLE

ROLE OF LOW MOLECULAR WEIGHT HEPARIN IN ADVERSE OBSTETRICAL OUTCOME IN-PATIENTS DUE TO OLIGOHYDROAMNIOS AND SEVERE IUGR

Naheed Akhtar, Nazli Hameed
Department of Obstetrics and Gynaecology, PAF Hospital Lahore, Pakistan

Background: Adverse obstetrical outcome means either patients with recurrent abortions or intrauterine death premature delivery due to foetal reasons in which foetus cannot survive *in utero* because of some hostile conditions like severe intrauterine growth retardation, severe oligohydramnios, or resistant umbilical artery blood flow. Low molecular weight heparin is recommended treatment in anti-phospholipid syndrome which improves perinatal outcome in patients with anti-phospholipid syndrome. **Methods:** This was an observational, intention-to-treat study conducted at Obs/Gyn Unit, PAF Hospital Lahore from March 2014 to March 2015. Low molecular weight heparin (LMWH) 40 mg subcutaneously daily was used from 16 weeks to 36 weeks of gestation. Hypertension and gestational diabetes was also addressed according to standard operative procedure of the hospital. **Results:** All 13 patients were delivered at 36 weeks of gestation by lower segment caesarean section. All neonates were delivered with Apgar score of 8/10–10/10. Carry home baby ratio was 100%. **Conclusion:** Low molecular weight heparin has definitive role in patients with adverse pregnancy outcome due to IUGR and oligohydramnios in the absence of APS and thrombophilias.

Keywords: IUGR, Low molecular weight heparin, anticoagulant therapy, adverse obstetrical outcome, oligohydramnios, anti-phospholipid antibody syndrome

Pak J Physiol 2015;11(1):17–9

INTRODUCTION

Severe Intrauterine Growth Retardation (IUGR) and oligohydramnios is a leading cause of perinatal mortality especially in patients with co-existing chronic hypertension, and/or diabetes mellitus which may be due to obesity, late marriages, elderly gravida, sedentary lifestyle, and polycystic ovarian syndrome (PCOS). Polycystic ovarian syndrome is more common in Southeast Asian population, incidence reported to be about 30%.[1] These co-morbidities increase the incidence of pregnancy induced hypertension, chronic hypertension with super imposed pregnancy induced hypertension, gestational diabetes, placental insufficiency.

Poor perinatal outcome seen in patients with anti-phospholipid syndrome (APS), in patients with systemic lupus erythematosus (SLE), recurrent miscarriages, thrombophilia etc. In these disorders because of increased hypercoagulability more than normal coagulation state of pregnancy will lead to thrombosis, placental insufficiency, decreased blood flow to placenta and foetus leading to decreased nutritional and oxygen supply to foetus which further causes IUGR, oligohydramnios, and foetal death.

Low molecular weight heparin (LMWH) is an excellent prophylaxes in APS, thrombophilias and recurrent miscarriages related to these disorders with improvement in perinatal outcome.[2–4]

Low molecular weight heparin is now preferred instead of unfractioned heparin because of its lesser side-effects, e.g., thrombocytopenia, osteoporosis haemorrhagic disorders, and allergic reactions, especially during pregnancy. It is also preferred because it has no teratogenic side-effects.[5]

Absence of transplacental passage of LMWH results in prevention of intrauterine foetal bleeding and neonatal haemorrhagic complications after delivery.[4]

Enthusiasm for exploring the potential benefits of LMWH is derived from its anticoagulant effect and improvement in perinatal outcome in patients with chronic hypertension without secondary causes. Low molecular weight heparin is excreted in breast milk in small amount that does not cause any haemorrhagic problem in infants. So breast feeding is not contraindicated in patients on thromboprophylaxes. Quantitative excretion is still to be established.[5]

The objective of the current study was to find the role low molecular weight heparin in adverse pregnancy out come due to severe IUGR and oligohydramnios in the absence of APS and thrombophilias.

SUBJECTS AND METHODS

This was an observational 'intention-to-treat' study conducted at Obs/Gyn Unit, Pakistan Air Force Hospital Lahore. The study was conducted in collaboration with Pathology (Haematology) Lab, Armed Forces Institute of Pathology (AFIP).

Thirteen patients were approached, convinced, and recruited for treatment with verbal

consent after explaining the objective, method, side-effects and failure of treatment. The patients included were para-3 or above with no alive issues. Out of the 13 patients, 12 were chronic hypertensives and 1 was diabetic along with chronic hypertension.

Anti-phospholipid syndrome was ruled out by anticardiolipin antibodies estimation, lupus anticoagulant antibodies thrice at monthly intervals according to nice guidelines.[7] These tests were negative in all patients. Test for thrombophilia, i.e., Antithrombin-III deficiency, protein s, and activated protein c deficiency were also negative.

Renal and hepatic disorders were ruled out with renal and liver function tests and renal/hepatic and abdominal ultrasonography. Previous history of deep vein thrombosis (DVT) and family history of DVT was also asked for and ruled out.

Patients received 40 mg low molecular weight heparin subcutaneously daily from 16 weeks of gestational up to 36 weeks of gestation. Initial follow-up visits were planned weekly till 20 weeks of gestation when prothombin time (PT), activated partial thromboplastin time (APTT) and platelet count were done on all visits. The visits were tailored fortnightly till 28 weeks of gestation with serial growth scans and ultrasonographic measurement of amount of liquor. After 28 weeks, follow-up visits were planned weekly for ultrasonology for biophysical profile score, growth scan, and umbilical artery Doppler study. At 32 weeks of gestation all patients were given injection dexamethasone intramuscularly as indoor treatment for foetal lung maturity.

The serial growth scan, amount of liquor, biophysical profile score were carried out at each visit after 28 weeks of gestation which were normal till delivery. The foetuses were also monitored by umbilical artery Doppler flow systolic/diastolic ratio at each visit, which was also normal, i.e., <2.6.

$$\text{Systolic-to-diastolic Ratio} = \frac{\text{Systolic peak velocity}}{\text{Diastolic peak velocity}}$$

Al patients were delivered at 36 weeks of gestation and LMWH was stopped 24 hours before surgery. All neonates were kept in neonatal intensive care unit for 24 hours under observation for any side-effects of LMWH.

Hypertension was controlled with α-methyldopa. Nifedipine was added when needed. All patients were educated for sign and symptoms of preeclampsia and asked to maintain record of their blood pressure. At each visit blood pressure was measured along with assessment of urine albumin, PT, APTT, platelet count, serum uric acid, and serum ALT. In diabetic patients blood sugar level was monitored and controlled with diet and Humulin insulin therapy.

RESULTS

The foetal biophysical profile score is tabulated as Table-1. All patients were delivered at 36 completed weeks of gestation through LSCS under spinal anaesthesia. No intraoperative or postoperative side-effects, e.g., excessive bleeding, oozing from surgery site, vaginal bleeding/oozing from placental bed or haematoma formation after spinal anaesthesia was seen in patients. All 13 neonates were delivered with Apgar score of 8/10–10/10. Carry home baby ratio was 100%.

Table-1: Foetal biophysical profile score

Variables	0 score	2 score
Foetal movements	Absent	Good gross body movements
Foetal tone	Absent	Extension flexion of limbs
Amount of liquor	Single liquor pocket of <2 Cm	Single liquor pocket of >2 Cm
Cardiotocography	Non-reactive CTG	Reactive CTG
Foetal breathing movements	Absent breathing movements	Present breathing movements

DISCUSSION

Chronic hypertension is now a globally rising issue, which has direct relationship with adverse pregnancy outcome which might be multifactorial, i.e., uncontrolled hypertension, placental insufficiency, poor blood supply through placenta, poor nutritional and oxygen supply.[7] To address this issue obstetricians have to improve perinatal outcome in this group of patients by using LMWH prophylacticaly.

All had normal foetal biophysical profile score, i.e., between 8/10 and 10/10 which indicates that LMWH plays an important role to prevent placental insufficiency in patients with adverse pregnancy outcome resulting in good perinatal outcome. The results were promising and it is evident that LMWH may play a good role in improving perinatal outcome in adverse pregnancy outcome in patients with IUGR and oligohydramnios which is due to factors other than APS and thrombophilia.[7]

Despite limited study in which only 13 patients were included, results were promising with prophylaxis LMWH use in patients with adverse pregnancy outcome due to severe IUGR and oligohydramnios because of chronic hypertension superimposed gestational hypertension. No side-effects with LMWH were observed in any of the participants.

All participants were South-Asian origin belonging to Pakistan. All participants were compliant with prescribed treatment and followed their visits according to advice.

Larger randomised cross-sectional studies are required involving multi-ethnic communities and multiple tertiary care centres to evaluate the results.

CONCLUSION

Low molecular weight heparin has definitive role in patients with adverse pregnancy outcome due to IUGR and oligohydramnios in the absence of APS and thrombophilias. There is need for further evaluation through extended studies.

ACKNOWLEDGEMENTS

We are grateful to our patients who received the treatment/medication at the hospital and materialised the study. We also thank our nursing team for training the patients to administer subcutaneously LMWH injections.

REFERENCES

1. Edmonds K. Dewhurst's Textbook of Obstetrics & Gynaecology, 8th ed. London: Black Well Publishers; 2012: 42–48, 519.
2. Rai R, Cohen H, Dave M, Regan L. Controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). BMJ 1997;314(7076):253–7.
3. Kupferminc MJ, Eldor A, Steinman N, Many A, Bar-Am A, Jaffa A, *et al*. Increased frequency of the genetic thrombophilia in women with complications of pregnancy. N Engl J Med 1999;340:9–13.
4. Gris JC, Mercier E, Quere I, Lavigne-Lissalde G, Cochery-Nouvellon E, Hoffet M, *et al*. Low-molecular-weight heparin versus low-dose aspirin in women with one fetal loss and a constitutional thrombophilic disorder. Blood 2004;103:3695–9.
5. James DK, Weiner CP, Street PJ, Gonik B. High risk pregnancy management options. 4th ed. Philadelphia: A Wolters Kluwer Company;2011:780–2, 184, 621–4.
6. Dimitrakakis C, Papageorgiou P, Papageorgiou I, Antzaklis A, Sakarelou N, Michalas S. Absence of transplacental passage of the low molecular weight heparin enoxaparin. Haemostasis 2000;30:243–8.
7. Richter C, Sitzmann J, Lang P, Weitzel H, Huch A, Huch R. Excretion of low molecular weight heparin in human milk. Br J Clin Pharmacol 2001;52(6):708–10.

Address for Correspondence:

Dr Naheed Akhtar, Gynaecologist, PAF Hospital, Lahore Cantt., Pakistan. **Cell:** +92-323-9428451
Email: adnan4094@gmail.com