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ORIGINAL ARTICLE

Safety and Efficacy of Low Molecular Weight Heparin Therapy During Pregnancy: Three Year Experience at a Tertiary Care Center

Singh Nilanchali · Varshney Priya · Tripathi Reva · Mala Y. M. · Tyagi Shakun

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Abstract
Purpose To evaluate safety and efficacy of low molecular weight heparin given for various indications during pregnancy.
Methodology A detailed retrospective analysis of all the patients who received low molecular weight heparin (LMWH) for various indications over a period of 3 years (2010–2012) at a tertiary care hospital in Northern India was performed.
Results Fifty-five patients received LMWH over the period of 3 years, for various indications. Enoxaparin (1 mg/kg body weight OD/BD subcutaneously) was used. The indications were valvular heart disease with valve replacement, atrial fibrillation, or thrombus in 60 % patients; chronic deep vein thrombosis (DVT) in 7 % patients; thrombophilia in 9.1 % patients; recurrent pregnancy losses in 18 % patients; and DVT prophylaxis in 5.5 % patients. Abortion was seen in 7.2 % patients; fetal growth restriction in 10.9 % patients; and oligohydramnios, preeclampsia, gestational hypertension, placenta previa, abruptio placentae, and postpartum hemorrhage in 1.8 % patients. Stillbirth occurred in 3.6 % patients. No thromboembolic event was noted in any of the patients. None of the patients had any documented thrombocytopenia or clinical fracture.
Conclusion Low molecular weight heparin can be used in pregnancy for various indications as an alternative to unfractionated heparin or warfarin as it is efficacious and safe.

Keywords Low molecular weight heparin · Safety · Pregnancy · Heart disease · Thrombophilias

Singh N. (✉), Senior Resident · Varshney P., Senior Resident · Tripathi R., Director Professor · Mala Y. M., Professor · Tyagi S., Associate Professor
Department of Obstetrics and Gynaecology, Maulana Azad Medical College and Associated Lok Nayak Hospital, MAMC Campus, Delhi Gate, New Delhi 110002, India
e-mail: nilanchalisingh@gmail.com

Introduction

Thromboembolism is the leading cause of maternal morbidity and mortality. The incidence of deep vein thrombosis and pulmonary embolism during pregnancy is 1 in 1,000 pregnancies. Unfractionated heparin is the drug of choice in pregnancy. Low molecular weight heparin fractions were first prepared in the late 1970s and early 1980s by fractionation of the crude unfractionated heparin. There are advantages of low molecular weight heparin over unfractionated heparin. It has a prolonged plasma half-life, once or twice daily dosing, more predictable anticoagulant response, no need for routine laboratory monitoring, lesser incidence of heparin-induced thrombocytopenia and osteoporosis, and fewer allergic skin reactions. Low molecular weight heparin therapy has widespread use during pregnancy for various indications. Concerns about its safety in pregnancy have been raised and there are various studies to

support its safety on maternal and fetal outcome [1–3]. There are no such studies from the Indian population; hence, we tried to evaluate safety and efficacy of low molecular weight heparin given during pregnancy for various indications over a period of 3 years in our hospital.

Methodology

A detailed retrospective analysis of all the patients who received low molecular weight heparin (LMWH) for various indications over a period of 3 years from the year 2010 to 2012 was done. The details were obtained from old case records of patients admitted in the maternity ward of a tertiary care hospital in Northern India. The characteristics of the patients, dosage, frequency, duration, and indication of LMWH were noted. Maternal complications in the form of hemorrhagic or thromboembolic event, thrombocytopenia, and other obstetric complications, if any, were evaluated. The obstetric and fetal outcomes were noted in terms of the period of gestation at delivery, live birth/stillbirth/abortions, birth weight, mode of delivery, Apgar score, and other fetal or neonatal complications, if any.

Results

Over the period of 3 years, 55 patients received LMWH for various indications. The characteristics of the patients are depicted in Table 1. Forty patients received LMWH both in the antepartum as well as the postpartum period, 12 patients received it in the antepartum period, and three patients in the postpartum period. Injection enoxaparin (Clexane) was used in all the patients as it is available in the hospital supply. The dosage of LMWH was 1 mg/kg body weight once or twice a day, depending on indication. The indication of LMWH therapy is depicted in Table 2. Patients with heart disease constituted 60 % of all patients who required LMWH therapy. The patients with heart disease, chronic deep vein thrombosis (DVT), and acquired or hereditary thrombophilias and those for prophylaxis of deep vein thrombosis were given enoxaparin 60 mg BD subcutaneously, whereas those with recurrent pregnancy losses were given 40 mg BD. The therapy was commenced at 6–8 weeks of gestation and was continued till 1 week postpartum in patients with heart disease, chronic DVT, and thrombophilias and then switched over to warfarin due to the feasibility of oral therapy. The patients with recurrent pregnancy losses without proven thrombophilias were instituted LMWH therapy till 36 weeks of gestation. Three post-Cesarean patients were given LMWH therapy for 1 week in the postpartum period as deep vein thrombosis prophylaxis as these patients were obese (BMI: 30.9–31.8 kg/m^2).

Table 1 Table depicting characteristics of the study population

Characteristics	Mean ± SD	Range
Age (in years)	26.2 ± 3.8	19–36
BMI (Kg/m^2)	19.4 ± 5.4	16–31.8
Obstetric history		
Gravidity	3.2 ± 1.5	1–6
Parity	1.2 ± 0.97	0–4
Abortions	1 ± 1.19	0–4
Live birth	0.6 ± 0.74	0–2
Duration of therapy (in days)	8.6 ± 5.6	1–32

The obstetric and fetal outcomes are depicted in Tables 3 and 4. Among the patients on LMWH therapy, 7.2 % patients had abortions. Two patients had missed abortions with no evidence of chorio-decidual bleed on ultrasound. One patient had chorio-decidual bleeding followed by a first trimester abortion and another patient had a large 4 × 5 cm retroplacental hematoma leading to a second trimester abortion at 18 weeks of gestation. One patient with rheumatic heart disease with thrombosis in the atria had severe fetal growth restriction followed by intrauterine fetal demise. Another patient with history of recurrent pregnancy losses had severe preeclampsia leading to abruptio placentae and fetal demise at 36 weeks. Postpartum hemorrhage was seen in one patient who was managed by oxytocics and uterine massage. No thromboembolic event noted in any of the patients in the study group. None of the patients had any documented thrombocytopenia, clinical fracture, or any allergic skin reactions.

Discussion

Safety and efficacy of LMWH have been studied by many authors, but data from the Indian population are lacking. Nelson-Piercy et al. [1] found that it is a safe and effective alternative to unfractionated heparin for obstetric thromboprophylaxis in high-risk women. Dolitzky et al. [2] reported high efficacy and few complications of enoxaparin in patients with recurrent pregnancy loss. Sanson et al. [3] reported low molecular weight heparins as an attractive alternative to unfractionated heparin due to their logistic advantages and their association with a lower incidence of osteoporosis and thrombocytopenia.

Unfractionated heparin (UFH) is used routinely in pregnant women after valvular heart surgery, though some studies have doubted its safety in pregnancy [4]. Lately, LMWH has also been used in these patients. We used enoxaparin in 28 patients with valvular replacement surgeries. One patient had chorio-decidual bleed in the first trimester followed by abortion. Another patient had

Table 2 Table depicting indication of low molecular weight heparin therapy in patients

Indication	Number of patients ($n = 55$)
Heart disease	
Mitral valve replacement	22 (40 %)
Double valve replacement	6 (11 %)
Rheumatic heart disease with atrial fibrillation	4 (7 %)
Rheumatic heart disease with thrombosis	1 (2 %)
Chronic deep vein thrombosis	4 (7 %)
Thrombophilias	
Inherited	2 (3.6 %)
Acquired	3 (5.5 %)
Recurrent pregnancy losses	10 (18 %)
Prophylaxis for deep vein thrombosis	3 (5.5 %)

postpartum hemorrhage which was managed by oxytocics. There was no evidence of any thrombotic event or heparin-induced thrombocytopenia in any of the patients. Hence, enoxaparin can be considered safe in such patients. Bucci et al. [5] compared the efficacy and safety of LMWH to unfractionated heparin after heart valve surgery and found it to be effective and safe with fewer thrombotic and bleeding events and thrombocytopenia. Saeed et al. [6] conducted a study to determine dose adjustment and safety of enoxaparin during pregnancy and reported it to be safe for women with mechanical prosthetic heart valves when there is dosage adjustment throughout pregnancy to maintain an anti-Xa of 1.0–1.2 U/mL. We used a 60 mg b.i.d. dosage in pregnant patients with valvular replacement and did not monitor them by anti-Xa levels due to cost constraints. We realized that monitoring with anti-Xa levels is not mandatory and LMWH can be used for these patients safely, especially in countries with low resource settings where monitoring may increase the monetary burden tremendously. We also used enoxaparin in a patient with atrial thrombus with a favorable outcome and she delivered uneventfully. The thrombus persisted in the postpartum state and the patient was referred to the cardiology department for further management.

We used enoxaparin 40–60 mg b.i.d. for 15 patients with thrombophilias and recurrent pregnancy losses. The live birth rate was 80 % and stillbirth rate was 6.6 % in these patients. There are many studies evaluating the effect of enoxaparin in patients with recurrent pregnancy losses and thrombophilias, but the data are predominantly uncontrolled with small series of patients. Brenner et al. [7] reported enoxaparin as a safe and effective therapy in prevention of pregnancy loss in women with inherited and acquired thrombophilia. According to another study, administration of enoxaparin to women with early recurrent fetal loss and impaired fibrinolytic capacity resulted in normalization of impaired fibrinolysis and conception in

Table 3 Obstetric outcomes in patients on LMWH therapy for various indications

	Heart disease ($n = 33$)	Chronic DVT ($n = 4$)	Thrombophilias ($n = 5$)	Recurrent pregnancy losses ($n = 10$)	DVT prophylaxis ($n = 3$)
Abortion	2 (6 %)	–	1 (20 %)	1 (10 %)	–
Intrauterine growth restriction	3 (9.1 %)	–	1 (20 %)	2 (20 %)	–
Oligohydramnios	–	–	1 (20 %)	–	–
Amniotic band	–	1 (25 %)	–	–	–
Preeclampsia	–	–	–	1 (10 %)	–
Gestational hypertension	–	1 (25 %)	–	–	–
Placenta previa	1 (3 %)	–	–	–	–
Abruptio placentae	–	–	–	1 (10 %)	–
Prematurity	2 (6 %)	–	1 (20 %)	1 (10 %)	–
Period of gestation at delivery (in weeks)	37 ± 7.2	39.1 ± 3.1	38.2 ± 3.4	36.4 ± 4.3	37.6 ± 4.5
Mode of delivery					
Vaginal	27 (81.8 %)	3 (75 %)	2 (40 %)	7 (70 %)	0
LSCS	6 (18.2 %)	1 (25 %)	2 (40 %)	1 (10 %)	3 (100 %)
Live birth	30 (90.9 %)	4 (100 %)	4 (80 %)	8 (80 %)	3 (100 %)
Stillbirth	1 (3 %)	–	–	1 (10 %)	–
Postpartum hemorrhage	1 (3 %)	–	–	–	–

Table 4 Fetal outcomes in patients on LMWH therapy for various indications

	Heart disease ($n = 33$)	Chronic DVT ($n = 4$)	Thrombophilias ($n = 5$)	Recurrent pregnancy losses ($n = 10$)	DVT prophylaxis ($n = 3$)
Apgar score at 5 min (<7)	1 (3 %)	–	1 (20 %)	–	–
Mean birth weight (in grams)	2560 ± 752	2810 ± 678	2610 ± 589	2590 ± 476	3010 ± 342
Neonatal Intensive Care Unit (NICU) admission	3 (9.1 %)	–	1 (20 %)	1 (20 %)	–
Respiratory distress	1 (3 %)	–	1 (20 %)	–	–
Transient Tachypnea of Newborn (TTN)	1 (3 %)	–	–	1 (20 %)	–
Neonatal sepsis	1 (3 %)	–	–	–	–

80 % and successful live birth in 81 % patients [8]. The LIVE ENOX study was a prospective, randomized, and multicentric trial comparing subcutaneous enoxaparin 40 mg/day with 80 mg/day (40 mg b.i.d.) in women with thrombophilia and previous pregnancy loss, and it concluded that both the doses are equally effective and safe. It was found that enoxaparin therapy significantly increases the live birth rate and decreases the rates of preeclampsia and placental abruption [9].

We used enoxaparin 60 mg b.i.d. in four patients with chronic deep vein thrombosis (DVT). Three among them had chronic DVT in the previous pregnancy or postpartum state and one had it after a prolonged surgery and bedridden stage. These patients were started on LMWH at 6–8 weeks of gestation and continued in the postpartum stage. The patients had no thrombotic and hemorrhagic complications. The American college of chest physicians recommends LMWH for the prevention and treatment of venous thrombosis in pregnant women instead of unfractionated heparin (Grade 1B). For pregnant women with acute venous thrombosis, they suggest that anticoagulants be continued for at least 6 weeks postpartum (for a minimum duration of therapy of 3 months) compared with shorter durations of treatment (Grade 2C) [10].

Puerperium is the period with the highest venous thromboembolism risk, which has been reported to be 25-fold higher than in nonpregnant women and more so in obese women (BMI >30 kg/m^2) [11]. We used enoxaparin for thromboprophylaxis for 7 days in three post-Cesarean patients as they were obese (BMI: 30.9–31.8 kg/m^2). LMWH is recommended for thromboprophylaxis in puerperium, at least 8 h after Cesarean section. Some guidelines recommend that the threshold for prescribing thromboprophylaxis should be lower in the postnatal period than that in the antenatal period [12, 13]. Some recommend that all women who have had Cesarean section either elective or emergency, and have one or more additional risk factors (including obesity), should receive thromboprophylaxis with LMWH for 7 days [12].

The obstetric outcomes as observed in this study were similar to prior studies. The stillbirth rate was 3.6 %; abortion rate was 7.2 %; fetal growth restriction was observed in 10.9 % patients; and oligohydramnios, preeclampsia, gestational hypertension, placenta previa, abruptio placentae, and postpartum hemorrhage were observed in 1.8 % patients. Figueiró-Filho et al. [14] used enoxaparin-based intervention in women with thrombophilias and reported a stillbirth rate of 3.6 %, abortion rate of 1.2 %, live birth rate of 70.2, and 4.8 % of patients developed preeclampsia/eclampsia.

Fetal and neonatal complications as seen in our study were comparable to other studies which consider LMWHs to be safe in pregnancy and lactation. As per our observation, no incidence of fetal hemorrhage was seen in any of the neonates. LMWH is the preferred agent for anticoagulation in pregnancy as there is no transplacental transfer due to their high molecular weight; hence, the incidence of fetal hemorrhage or teratogenicity is not increased [15]. The live birth rate in our study was 89 % in all patients on enoxaparin therapy and 80 % in patients with thrombophilia and recurrent pregnancy losses receiving this therapy. In another study, live births were reported in 94.7 % of pregnancies in women receiving enoxaparin therapy and in 85.4 % in those receiving LMWH for recurrent pregnancy loss [15].

The limitation of this study is that it is an uncontrolled study based on retrospective evaluation with a small study population. Another major limitation is the heterogeneity of indications for LMWH therapy in the patients included in the study. We present these data as studies regarding LMWH use in pregnant Indian women are lacking. It is not possible to comment upon the exact effect of LMWH therapy on maternal and fetal outcomes for various indications, and hence randomized, controlled trials are indicated.

Conclusion

Low molecular weight heparin is a safe and efficacious alternative to unfractionated heparin and warfarin in pregnancy and breast feeding. It can be used for various indications like valvular heart disease with valve replacement, atrial fibrillation and thrombus formation, thrombophilias, recurrent pregnancy losses, and prophylaxis or treatment of deep vein thrombosis.

Conflict of Interest The authors declare no conflict of interest.

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