ORIGINAL RESEARCH

Role of Low Molecular Weight Heparin in Women with Unexplained Recurrent First Trimester Miscarriage in India

[1]Dr. Farah Nabi, [2]Dr. Tahira Akhter, [3]Dr. Fehmeedah Banoo

[1]Assistant Professor, Department of Obstetrics and Gynaecology, Govt. Medical College, Baramulla, Jammu and Kashmir, India
[2,3]Assistant Professor, Department of Anesthesiology, Govt. Medical College, Baramulla, Jammu and Kashmir, India

Corresponding Author
Dr. Fehmeedah Banoo
Assistant Professor, Department of Anesthesiology, Govt. Medical College, Baramulla, Jammu and Kashmir, India

Received: 09 March, 2023 Accepted: 12 April, 2023

ABSTRACT

Background: Recurrent miscarriage (RM) is a distressing condition affecting 1-5% of couples experiencing infertility and 12-15% of pregnancies. Many cases go unrecognized due to losses occurring before clinical recognition, and the etiology of recurrent first-trimester miscarriage (RFM) remains unclear. Abnormal coagulation has been implicated in RFM, leading to the investigation of low molecular weight heparin (LMWH) as a potential intervention. However, research on LMWH's role in the Indian population, with its unique genetic and cultural factors, is limited. This study aims to evaluate the effectiveness and safety of LMWH in Indian women with unexplained RFM, providing insights into pregnancy outcomes and complications. **Methods:** This prospective hospital-based study was conducted over a period of two years. The participants consisted of pregnant women in their first trimester, with unexplained recurrent first trimester miscarriage. A total of 154 participants were monitored throughout their entire pregnancy period. The intervention involved the administration of low molecular weight heparin (LMWH) to the study participants at a prescribed standardized dosage. The primary outcome measures were the incidence of successful ongoing pregnancies beyond 20 weeks of gestation and the live birth rate. **Results:** The study included 154 pregnant women with unexplained recurrent first-trimester miscarriage. Most participants (83.1%) had no previous live births, and a significant proportion had a history of multiple previous abortions. Antiphospholipid syndrome (APLS) was identified in 51.3% of the participants, and specific subgroups of antiphospholipid antibodies (APLA) were found in 42.2% of the cases. In our study 89% pregnant women (137) had live births while 11% pregnant women (17) experienced abortions. Adverse drug reaction included allergic skin reactions in 1.3% of the participants and subcutaneous bruises in 3.2% of the participants. **Conclusion:** The findings of this study hold the potential to enhance our understanding of the efficacy, safety, and feasibility of LMWH therapy, ultimately offering new avenues for improving reproductive outcomes and alleviating the emotional burden experienced by couples affected by unexplained RFM in India.

Keywords: LMWH, Pregnancy, First trimester, recurrent abortions, miscarriage

INTRODUCTION

Recurrent miscarriage, defined as the loss of three or more consecutive pregnancies before 20 weeks of gestation, presents a distressing and perplexing problem for both patients and healthcare providers Recurrent pregnancy loss (RPL) accounts for approximately 1-5% of couples experiencing infertility and 12-15% of all pregnancies. Estimating the true incidence of RPL is challenging due to many losses occurring before clinical recognition, sometimes even before the first missed period. Out of all pregnancies, around 70% of affected females do not report their miscarriages. Among them, approximately 50% experience spontaneous miscarriage before the first menstrual cycle, while another 20% go unnoticed clinically [1].

Only about 30% of cases are recognized through clinical, radiological (such as the presence of an intrauterine gestational sac), histopathological, or biochemical (detecting viable levels of b-HCG) evaluations. Although various etiological factors, such as chromosomal abnormalities, anatomical abnormalities, endocrine disorders, and immunological abnormalities, have been implicated in

recurrent miscarriage, a considerable number of cases still elude clear explanation, leading to the classification of Recurrent First Trimester Miscarriage (RFM) [2,3].

In recent years, emerging evidence has suggested a potential association between abnormal coagulation and RFM. The intricate balance between coagulation and anticoagulation systems plays a crucial role in maintaining the placental vascular bed and ensuring uninterrupted blood flow to the developing fetus[4]. Perturbations in this delicate balance may lead to compromised uteroplacental circulation, resulting in early pregnancy loss. Consequently, anticoagulant therapies, particularly low molecular weight heparin (LMWH), have been proposed as a possible intervention to address coagulation abnormalities and improve pregnancy outcomes in women with RFM [5].

LMWH, a derivative of unfractionated heparin, exhibits several advantageous properties, including a more predictable pharmacokinetic profile, reduced risk of osteoporosis and heparin-induced thrombocytopenia, and simplified subcutaneous administration [6]. Moreover, LMWH has been shown to possess potential immunomodulatory effects, which may further contribute to its efficacy in recurrent miscarriage [7]. While evidence from various studies has demonstrated the beneficial impact of LMWH in women with URM, the majority of research has been conducted in Western populations, with limited studies exploring its role specifically in the Indian context.

India, with its diverse genetic and cultural landscape, represents a unique demographic for studying the impact of LMWH on RFM. Genetic and environmental factors, including variations in thrombophilic gene mutations, dietary habits, and lifestyle practices, may influence the pathogenesis and response to therapeutic interventions in this population [8,9]. Therefore, it is imperative to investigate the role of LMWH in Indian women with unexplained recurrent first trimester miscarriage, aiming to provide valuable insights into its effectiveness, safety, and potential benefits in this specific population. Therefore, this research article aims to critically evaluate the role of LMWH in women with unexplained RFM in the Indian population. By conducting a prospective study, we aim to to explore the impact of LMWH on pregnancy outcomes, including live birth rates, recurrent miscarriage rates, and maternal and fetal complications.

MATERIALS and METHODS

Study Design

This study employed a hospital-based prospective design and was conducted in North Kashmir, India. The research was carried out in a tertiary care hospital for 2 years between April 2021 to March 2023.

Participants

The participants included pregnant women (aged between ≥ 18 and< 35 years) in first trimester with unexplained recurrent first trimester miscarriage who sought medical care at the hospital during the study period. The inclusion criteria were as follows: (1) history of at least two consecutive first trimester miscarriages, (2) absence of known causes of recurrent miscarriage such as chromosomal abnormalities, anatomical abnormalities, or endocrine disorders, and (3) willingness to provide informed consent to participate in the study. Participants with known medical conditions such as thrombophilia, antiphospholipid syndrome, or other significant comorbidities were excluded from the study.

Sample Size Calculation

The sample size was determined based on an estimated effect size, statistical power, and significance level. A priori power analysis indicated that a minimum sample size of 154 participants would be required to achieve adequate statistical power for the primary outcomes. So, a total of 154 patients were monitored throughout their entire pregnancy period

Intervention

The intervention under investigation was the administration of low molecular weight heparin (LMWH) to the study participants. Only patients who adhered to the prescribed standardized dosage of the study medication, a daily subcutaneous dose of enoxaparin (LMWH) at 40 mgsc, upon confirmation of fetal viability through ultrasound at 6 weeks of gestation, were monitored until the completion of their pregnancy.This treatment regimen was maintained until 34 completed weeks of gestation.

Follow up

Women who received LMWH were instructed on self-administration of subcutaneous injections in the anterolateral abdominal wall, alternating between the right and left sides. PT, APTT and INR were assessed in every trimester. Adherence to the medication regimen was confirmed through biweekly telephone interviews during the initial 4 weeks. Prenatal follow-up visits were scheduled at 4-week intervals until 32 weeks of gestation, followed by visits every 2 weeks between 32 and 36 weeks. If the pregnancy continued to term, weekly follow-up visits were conducted until delivery to assess fetal growth, fetal well-being, and monitor any potential side effects of the medication.Pregnancy was allowed to proceed until 37 completed weeks of gestation, and elective caesarean section was performed at that point. However, if any emergency situations arose before reaching 37 weeks, the pregnancy could be terminated earlier.

Data Collection

Data were collected through structured interviews, medical record review, and laboratory investigations. The following information was recorded for each participant: demographic characteristics, obstetric history, clinical presentation, laboratory test

results[routine blood test, blood sugar, TSH,prolactin, antiphospholipid antibodies subgroups, lupus anticoagulant (LA), anticardiolopin antibody(ACLA) and antinuclear antibody (ANA)], ultrasound findings, and any adverse events related to LMWH administration. Data collection was performed by trained research personnel using standardized data collection forms.

Outcome Measures

The primary outcome measure was the incidence of successful ongoing pregnancies, defined as pregnancies that progressed beyond 20 weeks of gestation and live birth rate. Secondary outcomes included maternal complications, such as thromboembolic events and bleeding complications, as well as fetal outcomes, including congenital anomalies and perinatal mortality.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study participants. Categorical variables were presented as frequencies and percentages, while continuous variables were reported as means with standard deviations or medians with interquartile ranges, as appropriate.

Ethical Considerations

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of [Approval number: IEC/323/2021]. Informed consent was obtained from all participants before their inclusion in the study.

RESULTS

In our study 154 pregnant women in first trimester were followed till 37 weeks for delivery outcomes. The mean age of the participants was 27.97 years with a standard deviation of 5.62. The mean Body Mass Index (BMI) was 25.76 kg/m2 with a standard deviation of 3.24. The majority of the participants (83.1%) had a parity of 0, indicating no previous live births, while 16.9% had a parity of 1 or more. Regarding the number of previous abortions, 31.2% had experienced 2 previous abortions, 33.8% had experienced 3, and 35.1% had experienced 4 or more. The mean number of previous abortions was 3.57 with a standard deviation of 1.27, and the mean gestational age (GA) of previous abortions was 7.21 weeks with a standard deviation of 2.65. Additionally, 35.1% of the participants had been diagnosed with polycystic ovary syndrome (PCOS), while the remaining 64.9% did not have PCOS (Table 1).

Table 1. Baseline characteristics of the enrolled pregnant women (N=154).

Baseline characteristics	Frequency	%
Mean age (in years)	27.97±5.62	
Mean Body Mass Index [BMI] (in Kg/m^2)	25.76±3.24	
Parity		
0	128	83.1
≥1	26	16.9
Number of previous abortions		
2	48	31.2
3	52	33.8
≥4	54	35.1
Mean Previous abortions	3.57±1.27	
Mean GA of previous abortion (in weeks)	7.21±2.65	
Polycystic ovary syndrome (PCOS)		
Yes	54	35.1
No	100	64.9

GA: gestational age

Among the participants, 29.2% tested positive for anticardiolipin antibodies (ACLA), while 18.8% tested positive for lupus antibodies (LA). The presence of antiphospholipid syndrome (APLS) was identified in 51.3% of the participants. Additionally, 42.2% of the participants tested positive for specific subgroups of antiphospholipid antibodies (APLA). Antinuclear antibodies (ANA) were found to be positive in 11.0% of the participants. Notably, 16.2% of the participants were positive for both ACLA and LA antibodies. In terms of diagnosis, 35.1% of the participants had no identifiable cause for their recurrent miscarriages (Table 2).

Table 2. Laboratoryprofile specific for recurrent abortions of the enrolled pregnant women (N=154).

Laboratory variables#	Frequency	%
ACLA positive	45	29.2
LA positive	29	18.8
APLS	79	51.3
APLA subgroups positive	65	42.2

ANA positive	17	11.0
ACLA±LA positive	25	16.2
No cause identified	54	35.1

ACLA: Anticardiolipin antibody, APLS: Antiphospholipid syndrome, LA: Lupus antibody, APLA: Antiphospholipid antibody subgroups positive, ANA: Antinuclear antibody

In our study 89% pregnant women (137) had live births while 11% pregnant women (17) experienced abortions. The mean duration of abortion was 10.12 weeks with a standard deviation of 4.26 weeks. The mean gestational age at delivery was 36.28 weeks with a standard deviation of 3.17 weeks. Among the births, 27.7% were classified as premature births occurring before 32 weeks, while 72.3% occurred on or after 32 weeks. The incidence of preeclampsia, a pregnancy complication characterized by high blood pressure, was found to be 5.8%. Intrauterine growth retardation (IUGR) was observed in 2.2% of the cases. Adverse drug reaction included allergic skin reactions in 1.3% of the participants and subcutaneous bruises in 3.2% of the participants. The mean birth weight of the newborns was 2739.65 grams with a standard deviation of 213.73 grams. Neonatal intensive care unit (NICU) admission was required for 7.3% of the newborns, while there were no cases of birth asphyxia or congenital anomalies observed (Table 3).

Table 3. Maternal and foetal outcome among the enrolled pregnant women.

Outcome variables	**Frequency**	**%**
Live birth	137	89
Abortion	17	11
Mean duration of Abortion (in weeks)	10.12±4.26	
Mean Gestation age (in weeks)	36.28±3.17	
Premature birth*		
<32 weeks	38	27.7
≥32 weeks	99	72.3
Incidence of Preeclampsia	9	5.8
IUGR*	3	2.2
Drug Adverse events		
Allergic skin reactions	2	1.3
Subcutaneous bruises	5	3.2
Mean birth weight (in grams)*	2739.65±213.73	
NICU admission	10	7.3
Birth asphyxia	0	0.0
Congenital anomaly	0	0.0

*N=137, IUGR: Intrauterine growth retardation, NICU: Neonatal intensive care unit

DISCUSSION

The present study aimed to evaluate the role of low molecular weight heparin (LMWH) in women with unexplained recurrent first-trimester miscarriage in India. Our findings provide valuable insights into the baseline characteristics, laboratory variables, and outcome measures of the enrolled pregnant women.

In our study 89% pregnant women (137) had live births while 11% pregnant women (17) experienced abortions. Yuksel et al., conducted a prospective observational study involving 150 women with a history of unexplained first-trimester pregnancy loss who received LMWH and they reported a live birth rate of 85% [10]. Cetin et al., conducted a study on 120 women with unexplained recurrent miscarriages, treated the patients with LMWH and they found live birth rate of 69.8% [11]. According to a study conducted by Monien et al., which included 164 women with early and late miscarriages, it was found that 83.8% of the women who received LMWH treatment had successful live births [12]. Similarly, Xu et al., conducted a hospital study involving 120 RFM patients and they reported pregnancy success rate of 90.00% [13]. Shaaban et al., conducted a randomized controlled trial involving 300 participants with unexplained recurrent pregnancy loss and they reported a live birth rate of 65.7% [14]. However, Pasquier et al., and Schleussner et al., in a multicenter randomized controlled trial among pregnant women with RFM, did not find a significant difference in the live birth rate between the LMWH and placebo groups ($p>0.05$) [15,16].

Women with a history of recurrent pregnancy loss are known to have a high incidence of late pregnancy complications. These complications include preterm contractions, preterm labor, preeclampsia, intrauterine growth restriction, low birth weight, and intrauterine fetal demise. It has been suggested that the underlying etiopathogenesis of RFM may contribute to the occurrence of these late pregnancy complications [17]. Therefore, interventions that effectively improve pregnancy outcomes in women with RFM are likely

to also reduce the risk of late pregnancy complications. In our study, Preeclampsia, a pregnancy complication characterized by high blood pressure, was observed in 5.8% of the participants. Intrauterine growth retardation (IUGR) was identified in 2.2% of the cases. The mean birth weight of the newborns was 2739.65 grams. Neonatal intensive care unit (NICU) admission was required for 7.3% of the newborns, while no cases of birth asphyxia or congenital anomalies were observed.

Schleusner et al., conducted a study and maternofoetal complications encompassed three instances of intrauterine fetal demise, nine cases of preeclampsia accompanied by HELLP syndrome, and eleven cases of intrauterine growth restriction caused by placental insufficiency [16].In the study conducted by Shaaban et al., the preeclampsia rates were 2.7% and fetal death rates were 13.7% [14].Han et al., conducted a study revealed a preeclampsia incidence of 5.6% and preterm birth of 21.7%, 10.6% were infants classified as small for gestational age [18]. Similar complications were reported in other studies [11,19,20]. Overall, LMWH treatment did not lead to an increase in late pregnancy complications among women with recurrent first trimester miscarriage.

LMWH, when used as an anticoagulant, demonstrates a remarkable level of safety compared to other forms of heparin. Nevertheless, it is important to monitor patients taking this medication for potential complications like bleeding, purpuric rash, thrombocytopenia, and osteoporosis [10,21,22]. It is crucial to conduct regular monitoring for adverse drug reactions since changes in blood characteristics during pregnancy may amplify the likelihood of such reactions when using LMWH. Furthermore, women using LMW heparin during pregnancy may face an increased risk of postpartum hemorrhage, which is a significant cause of maternal morbidity and mortality globally [23,24].In our study, allergic skin reactions (1.3%) and subcutaneous bruises (3.2%), were reported as adverse events of LMWH. According to Li et al., adverse effects were observed sporadically in women who underwent LMWH treatment for the management of unexplained recurrent pregnancy loss [20].In a study conducted by Xu et al., the incidence of adverse drug reactions was 20.00% in women who received LMWH[13].In a separate study conducted by De Jong et al., it was observed that nearly 40% of patients who received LMWH treatment experienced local skin reactions such as pain, itching, and swelling at the injection site [19]. But according to Monien et al., there were no significant adverse effects associated with the use of LMWH in women receiving treatment for unexplained recurrent pregnancy loss [12].

LIMITATIONS

Several limitations should be acknowledged, including the single-center design, the potential for selection bias, and the absence of a control group. These limitations may affect the generalizability of the findings.

CONCLUSION

In conclusion, this research article aims to contribute to the existing knowledge regarding the role of LMWH in the management of unexplained RFM in the Indian population. The findings of this study hold the potential to enhance our understanding of the efficacy, safety, and feasibility of LMWH therapy, ultimately offering new avenues for improving reproductive outcomes and alleviating the emotional burden experienced by couples affected by unexplained RFM in India.

REFERENCES

1. Wang X, Chen C, Wang L, et al. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. FertilSteril 2003;79(3):577–584.
2. Brenner B, Hoffman R, Blumenfeld Z, Weiner Z, Younis J. Gestational outcome in thrombophilic women with recurrent pregnancy loss treated by enoxaparin. Thromb Haemost. 2000;83(5):693-697.
3. Regan L, Backos M, Rai R. The Investigation and Treatment of Couples with Recurrent First trimester and Second-trimester Miscarriage. Royal College of Obstetricians and Gynaecologists. 2011.
4. Clark P, Walker ID, Langhorne P, et al. SPIN (Scottish Pregnancy Intervention) study: a multicenter, randomized controlled trial of low-molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. Blood. 2010;115(21):4162-4167.
5. Brenner B. Inherited thrombophilia and pregnancy loss. Best Pract Res Clin Haematol. 2003;16(2):311-320.
6. Giancotti A, La Torre R, Spagnuolo A, et al. Efficacy of three different antithrombotic regimens on pregnancy outcome in pregnant women affected by recurrent pregnancy loss. J MaternFetal Neonatal Med. 2012;25(7):1191-1194.
7. Farquharson RG, Jauniaux E, Exalto N; ESHRE Special Interest Group for Early Pregnancy (SIGEP). Updated and revised nomenclature for description of early pregnancy events. Hum Reprod. 2005;20(11):3008-3011.
8. Rohilla, M, Muthyala T. Recurrent Pregnancy Loss (RPL) - Causes and Management. J Gynecol Neonatal Biol. 2017;3:5-8.
9. Chakraborty P, Goswami SK, Rajani S, et al. Recurrent pregnancy loss in polycystic ovary syndrome: Role of hyperhomocysteinemia and insulin resistance. PLoS One. 2013;8:e64446.
10. Yuksel H, Kayatas S, Boza AT, Api M, Ertekin AA, Cam C. Low molecular weight heparin use in unexplained recurrent miscarriage. Pak J Med Sci. 2014;30:1232-1237.
11. Cetin O, Karaman E, Cim N, et al. The impact of low molecular weight heparin on obstetric outcomes among unexplained recurrent miscarriages complicated with methylenetetrahydrofolate reductase gene polymorphism. Ginekol Pol. 2017;88:260-265.
12. Monien S, Kadecki O, Baumgarten S, Salama A, Dörner T, Kiesewetter H. Use of heparin in women with early and late miscarriages with and without

thrombophilia. Clin ApplThrombHemost. 2009;15:636-644.
13. Xu GL, Hu XF, Han YM, Wei AW. Clinical efficacy of low molecular heparin on unexplained recurrent spontaneous abortion. Clin Lab. 2018;64:1037-1040.
14. Shaaban OM, Abbas AM, Zahran KM, Fathalla MM, Anan MA, Salman SA. Low-molecular-weight heparin for the treatment of unexplained recurrent miscarriage with negative antiphospholipid antibodies: a randomized controlled trial. Clin ApplThrombHemost. 2017;23:567-572.
15. Pasquier E, de Saint Martin L, Bohec C, et al. Enoxaparin for prevention of unexplained recurrent miscarriage: a multicenter randomized double-blind placebo-controlled trial. Blood. 2015;125:2200-2205.
16. Schleussner E, Kamin G, Seliger G, et al. Low-molecular-weight Heparin for women with unexplained recurrent pregnancy loss: a multicenter trial with a minimization randomization scheme. Ann Intern Med. 2015;162:601-609.
17. Brigham SA, Conlon C, Farquharson RG. A longitudinal study of pregnancy outcome following an idiopathic recurrent miscarriage. Hum Reprod. 1999;14:2868-2871.
18. Han AR, Ahn H, Vu P, et al. Obstetrical outcome of anti-inflammatory and anticoagulation therapy in women with recurrent pregnancy loss or unexplained infertility. Am J Reprod Immunol. 2012;68:418-427.
19. De Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin and heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia. Cochrane Database Syst Rev. 2014;2014:CD004734.
20. Li J, Gao YH, Xu L, Li ZY. A meta-analysis of heparin combined with aspirin versus aspirin alone for unexplained recurrent spontaneous abortion. Gynecol Obstet. 2020;151:23-32.
21. Onishi A, St Ange K, Dordick JS, Linhardt RJ. Heparin and anticoagulation. Front Biosci. 2016;21:1372-1392.
22. Karadağ C, Yoldemir T, Karadağ SD, İnan C, Dolgun ZN, Aslanova L. Obstetric outcomes of recurrent pregnancy loss patients diagnosed with inherited thrombophilia. Irish J Med Sci. 2017;186:707-713.
23. Wang EH, Marnoch CA, Khurana R, Sia W, Yuksel N. Haemorrhagic complications of peripartum anticoagulation: a retrospective chart review. Obstet Med. 2014;7:77-83.
24. Knol HM, Schultinge L, Veeger NJ, Kluin-Nelemans HC, Erwich JJ, Meijer K. The risk of postpartum hemorrhage in women using high dose of low-molecular-weight heparins during pregnancy. Thromb Res. 2012;130:334-338.