Role of Low Molecular Weight Heparin in Unexplained Recurrent Pregnancy Loss

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ABSTRACT

Objective: To evaluate the effectiveness of low molecular weight heparin (LMWH) in unexplained recurrent pregnancy loss (URPL).
Study Design: Open-labelled, single-centre, randomised controlled trial.
Place and Duration of the Study: Department of Obstetrics and Gynaecology, DG Khan Hospital, Dera Ghazi Khan, Pakistan, from June 2023 to December 2024.
Methodology: One hundred and seventy pregnant women aged 18-44 years with a gestational age exceeding 8 weeks and a history of three or more consecutive first-trimester pregnancy losses were randomly assigned to one of two groups using the sealed envelope lottery method. The LMWH group (n = 85) received a daily subcutaneous injection of 40 mg LMWH, while the placebo group (n = 85) was given a multivitamin tablet as a placebo. The primary outcome was assessed in terms of efficacy, defined as live births occurring after reaching 24 weeks of gestation. Secondary outcomes included both maternal and foetal health outcomes. Numeric data were compared by applying the Mann-Whitney U test, while categorical data were compared by employing the Chi-square test. For all inferential statistics, a value of $p < 0.05$ was considered statistically significant.
Results: In a total of 170 women, the median age was 32.00 (30.00-35.00) years. In the LMWH group, the proportion of live-births was 88.0% *versus* 73.4% in the placebo group ($p = 0.019$). It was found that the proportion of caesarean section was significantly higher among women of the LMWH group (72.6% *vs*. 51.7%, $p = 0.014$). The proportion of premature birth was significantly high in placebo group (25.9% *vs*. 9.6%, $p = 0.013$).
Conclusion: This study demonstrates that the LMWH is associated with a significantly higher live birth rate in women with RPL, without increasing the risk of adverse maternal and neonatal outcomes.

Key Words: *Heparin, Gestational age, Low birth weight, Placebo, Pregnancy loss*.

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INTRODUCTION

Recurrent pregnancy loss (RPL) is a major concern in gynaecology, posing both emotional and medical challenges.[1] RPL is defined as the spontaneous termination of ≥3 consecutive pregnancies within the 1st trimester, with the same biological father involved in each case.[2] RPL affects 2-4% pregnancies.[3] RPL can be attributed to several factors, including uterine anatomical anomalies, endocrine, hormonal, or biochemical imbalances, and genetic or chromosomal disorders.[4] While numerous causes of RPL are treatable, approximately 50% of cases remain unexplained.[5]

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The term unexplained RPL (URPL) is described as the spontaneous loss of ≥3 consecutive pregnancies without any recognisable cause.[6] Research indicates that factors such as placental thrombosis, vascular endothelial growth factor dysfunction, and maternal-foetal immunological issues may contribute to URPL. Proinflammatory changes and complement activation have also been consistently observed in URPL-affected women.[7] There is a growing evidence linking methylene tetrahydrofolate reductase (MTHFR) gene polymorphisms with URPL.[8]

Many forms of heparin-based medications, such as unfractionated heparin (UFH), low molecular weight heparin (LMWH), and synthetic heparins, are currently used in clinical practice, and these medicines are designated to be vitally important for the treatment of disorders such as thrombosis or embolism.[9] The use of heparin is associated with risks including bleeding, heparin-induced thrombocytopaenia, and osteoporosis, which require careful monitoring.[10] The development of LMWH, which offers a longer half-life, better bioavailability, and a more stable dose-response relationship, has enhanced its safety profile.[11] LMWH is similarly

effective in managing and preventing various coagulation disorders due to its anticoagulant and anti-inflammatory effects and has been investigated for treating URPL linked to both thrombophilic and non-thrombophilic conditions.[8,9,12] A local study from Islamabad, Pakistan, reported that the proportion of live birth rates among URPL, with and without LMWH, were 78.8% and 73.8% (p = 0.574).[13] A study from Turkiye reported live-birth rates with LMWH and placebo as 85.0% *vs.* 66.0% (p = 0.007).[14] Several studies have reported outcomes such as live birth rates and the incidence of maternal and foetal complications, with clear variations in results.

The present study aimed to determine whether LMWH administration results in higher live birth rates or reduced miscarriage rates compared to placebo, as well as various maternal and foetal outcomes in this set of patients. It was hypothesised that if this study demonstrates positive results, it could lead to significant advancements in both clinical practice and further research. The findings could inform new treatment protocols, allowing for more personalised and effective management of URPL cases. This would improve patient counselling and risk management strategies, potentially reducing miscarriage rates and associated psychological distress. On the research front, positive results might stimulate further investigations into the mechanisms by which LMWH influences pregnancy outcomes, explore its long-term effects, and compare it with other treatments.

METHODOLOGY

This open-labelled, single-centre, randomised controlled trial was conducted at the Department of Obstetrics and Gynaecology, Hospital, DG Khan Hospital, Dera Ghazi Khan, Pakistan, from June 2023 to December 2024 after getting approval from the Institutional Ethical Committee. The study protocol of this trial was registered with clinical trial registration number: NCT06484634. Given the expected live birth rates of 85.0% with LMWH and 66.0% without LMWH,[14] and aiming for a 95% confidence level with 80% statistical power, the calculated sample size (online OpenEpi sample size calculator) was determined to be 170, with 85 participants allocated to each group. Simple random sampling technique was adopted. Informed and written consents were obtained from all study participants. Participant identifiers were anonymised using unique study codes to maintain confidentiality. Participants were ensured about their data confidentiality and the voluntary nature of participation.

The inclusion criteria comprised pregnant women aged 18-44 years with a gestational age beyond 8 weeks and ≥3 consecutive first-trimester pregnancy losses. Women with thrombophilia and anti-phospholipid syndrome, with any kind of diabetes mellitus, and with a known sensitivity to the study medicines were excluded. Those with a known genetic cause, anatomical cause, or hormonal cause of RPL were also not included.

Upon enrolment, a comprehensive medical history and thorough clinical examination were conducted. Participants were randomly assigned using a lottery method to either the LMWH group (n = 85), who received a daily subcutaneous injection of 40 mg LMWH, or the placebo group (n = 85), who received a multivitamin tablet as a placebo. Women were monitored at the antenatal clinic every 6 weeks. The primary outcome was measured by the efficacy of treatment, defined as live births occurring after 24 weeks of gestation. Secondary outcomes included maternal and foetal outcomes. Maternal outcomes included mode of delivery, preeclampsia, foetal growth restriction (FGR), and gestational age at the time of delivery. Foetal outcomes including, gender, low birth weight (LBW), premature birth, and need for neonatal intensive care unit (NICU) were also noted. LBW was labelled as birth weight below 2,500 grams. Premature birth was labelled as birth below 32 weeks of gestation. Throughout the study period, participating females were contacted telephonically and reminded of the scheduled follow-up visit. All the relevant data were collected by the designated obstetricians of the department of the study place. Obstetricians were responsible for patient recruitment, clinical care, and intervention administration, and outcome evaluations. All data were collected and stored in a secure, digital database accessible only to the research team. A special proforma was designed to record all study data. Figure 1 shows CONSORT flow diagram.

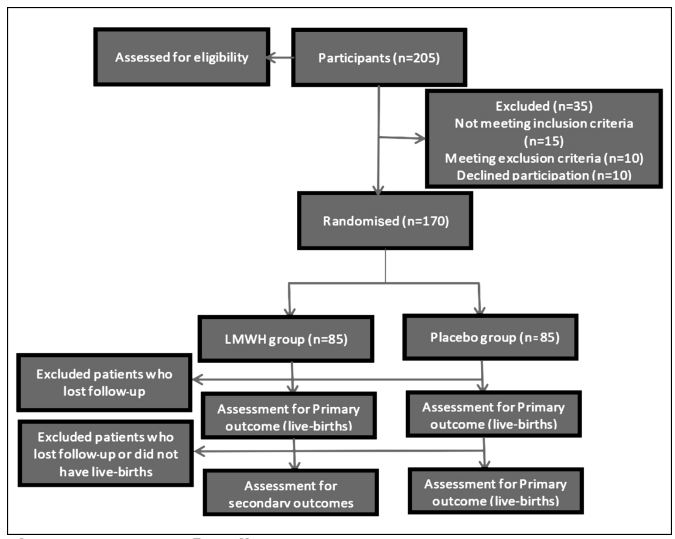

Figure 1: CONSORT flow diagram.

Data were analysed using IBM-SPSS Statistics, version 26.0. Categorical data were shown as frequency and percentage. Normality distribution of the data was checked using Shapiro-Wilk's test. Mean and standard deviation were shown for quantitative data. Chi-square test was applied for the comparison of categorical data. Independent samples t-test (for normally distributed data), or Mann-Whitney U test (for non-normally distributed data), were applied to compare quantitative data between groups. For all inferential statistics, $p < 0.05$ was taken as significant.

Table I: Comparison of baseline characteristics of patients (n = 170).

Baseline characteristics	Groups		p-value
	LMWH (n = 85)	Placebo (n = 85)	
Age (years)	32.00 (29.00-35.00)	32.00 (30.00-35.00)	0.761*
Body mass index (kg/m^2)	26.00 (25.00-28.00)	26.00 (25.00-27.00)	0.870*
Number of past miscarriages	3.00 (3.00-4.00)	3.00 (3.00-4.00)	0.951*
Gestational age (weeks)	11.00 (9.00-12.00)	11.00 (9.75-13.00)	0.478*
Residence			0.874#
Rural	54 (63.5%)	53 (62.4%)	
Urban	31 (36.5%)	32 (37.6%)	

**Mann-Whitney U test applied; #Chi-square test applied.*

Table II: Comparison of primary outcome (live-births) among women of both study groups (n = 162).

Live birth	Groups		p-value
	LMWH (n = 83)	Placebo (n = 79)	
Yes	73 (88.0%)	58 (73.4%)	0.019*
No	10 (12.0%)	21 (26.4%)	

**Chi-square test applied.*

Table III: Comparison of secondary outcomes among women of both study groups (n = 131).

Secondary outcome variables			Groups		p-value
			LMWH (n = 73)	Placebo (n = 58)	
Maternal outcomes	Delivery mode	Caesarean section	53 (72.6%)	30 (51.7%)	0.014*
		Vaginal delivery	20 (27.4%)	25 (48.3%)	
	Pre-eclampsia		9 (12.3%)	3 (5.2%)	0.158*
	Foetal growth restriction		2 (2.7%)	1 (1.7%)	0.700*
	Gestational age at the time of delivery (weeks)		36.00 (35.00-38.00)	37.00 (31.00-38.00)	0.461#
Neonatal outcomes	Premature birth		7 (9.6%)	15 (25.9%)	0.013*
	Gender	Boy	43 (58.9%)	41 (70.7%)	0.162*
		Girl	30 (41.1%)	17 (29.3%)	
	Low birth weight		30 (41.1%)	24 (41.4%)	0.974*
	NICU admissions		13 (17.8%)	16 (27.6%)	0.181*

**Mann-Whitney U test applied; #Chi-square test applied.*

RESULTS

In a total of 170 women, the median age and BMI were 32.00 (30.00-35.00) years and 26.00 (25.00-28.00) kg/m^2, respectively. The median previous consecutive miscarriages was 3.00 (3.00-4.00). The median gestational age at the time of enrolment was 11.00 (10.00-12.00) weeks. Table I is showing comparison of baseline characteristics of women in both study groups, and it was found that no statistically significant differences existed.

Two women in the LMWH group, and 6 in the placebo group lost follow-ups so they were excluded from the final analysis. In the LMWH group, the proportion of live-births was 88.0% *versus* 73.4% in the placebo group (p = 0.019) as shown in Table II.

Women in both study groups who had live-births (n = 131) were further evaluated for maternal and neonatal outcomes. It was found that the proportion of caesarean sections was significantly higher among women of the LMWH group in comparison to those in the placebo group (72.6% *vs*. 51.7%, p = 0.014). Gestational age at the time of delivery (p = 0.461), the occurrence of pre-eclampsia (p = 0.158), and FGR (p = 0.700) were statistically similar in both study groups. The proportion of premature birth was statistically high in the placebo group (25.9% *vs*. 9.6%, p = 0.013). The occurrence of low birth weight (p = 0.974) and need for NICU admission (p = 0.181) were statistically similar among females of both study groups, and the details are shown in Table III.

DISCUSSION

These findings highlight the potential benefits of LMWH in enhancing live-birth rates in RPL cases. The literature on the use of LMWH in URPL presents mixed results. While retrospective observational studies have reported better pregnancy outcomes with LMWH,[15,16] meta-analyses of prospective randomised trials have not consistently confirmed this benefit.[17] In comparison to the SPIN trial and ALIFE trial,[18,19] which presented similar outcomes in LMWH and control groups, this study demonstrates a positive impact of LMWH on live-birth rates. SPIN trial,[18] which included surveillance alone as the control, reported pregnancy loss rates of 20% in the surveillance group and 22% in the LMWH plus aspirin group, highlighting the need for further research to identify specific subgroups that may benefit from LMWH therapy. Yuksel *et al*. found significantly lower abortion rates and higher live-birth rates in the LMWH group in comparison to controls, which supports the present finding of improved live-birth rates with LMWH treatment.[14] Higher live-birth rate among females of the LMWH group aligns with the findings

of Schleussner *et al*.,[20] who reported 86.0% of women in the LMWH group. However, unlike this study, Schleussner *et al*. noted a clear difference in live-birth rates between the LMWH and controls, with their study showing an absolute difference of -0.7 percentage points (p = 0.84). This discrepancy could be attributed to differences in study design, population characteristics, or the definition of primary outcomes. This study revealed an important addition to the existing body of evidence that may suggest LMWH as an effective option aiming to improve live-birth rates. The anti-inflammatory and anti-complement properties of heparin, in addition to its anticoagulant effects, may contribute to its efficacy in improving pregnancy outcomes.[21]

This study suggests that while LMWH may improve live birth rates, it may also be associated with a significantly higher likelihood of caesarean delivery. This could be due to cautious clinical management of pregnancies treated with LMWH, aiming to mitigate potential complications associated with anticoagulation therapy. While studying women in RPL, Yuksel *et al*., from Turkiye[14] reported that the caesarean section rate was 42% among females in the LMWH group *versus* 20% in the placebo group (p = 0.06), and these findings are somewhat similar to what is documented in this research. The higher caesarean rate in this study warrants further investigation to understand the underlying reasons and to optimise delivery planning for women receiving LMWH.

Gestational age at delivery, pre-eclampsia, and FGR were alike in LMWH and placebo groups in this study, indicating that LMWH did not significantly impact these outcomes. This study found a significantly lower rate of premature births in the LMWH group compared to the placebo group, which contrasts with the findings of Schleussner *et al*., who reported similar rates of premature births in both groups.[20] This difference might be due to variations in study populations and clinical practices. Regarding neonatal outcomes, the occurrence of LBW and the need for NICU admission were similar between the two groups in this study. This aligns with the findings of Yuksel *et al*.,[14] who noted similar birth weights and NICU admissions between the LMWH and control groups.

LMWH was used based on its proposed role in improving implantation and placental development by enhancing uteroplacental circulation and modulating immune function, which may benefit women with URPL.[22] The selected dose of 40 mg once daily is consistent with recommendations from the American College of Obstetricians and Gynaecologists (ACOG) and other published studies for prophylactic use in pregnancy.[13,23] No dose escalation was indicated, as none of the participants had underlying thrombophilia or other high-risk factors requiring therapeutic dosing.

The absence of large sample size and a single-centre study site may reflect restriction in the generalisability of the present results. The exclusion of women who lost follow-ups may introduce bias. Future studies can aim to verify the findings of this study in larger, multi-centre studies to confirm the efficacy of LMWH in improving live-birth rates and to explore its impact on other maternal and neonatal outcomes.

CONCLUSION

This study demonstrates that LMWH is associated with a significantly higher live-birth rate in women with URPL, without increasing the risk of adverse maternal and neonatal outcomes. The higher rate of caesarean sections in the LMWH group highlights the need for careful delivery planning in these patients. Further research is needed to optimise its use and to identify specific patient subgroups that may benefit the most from this treatment.

ETHICAL APPROVAL:
Ethical approval was obtained from the Ethical Review Committee of the DG Khan Medical College (Letter No: 115; Dated: 31-05-2023) (Clinical Trial Registration: NCT0648 4634).

PATIENTS' CONSENT:
Informed and written consents were obtained from all study participants.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
RP: Conception of the idea, literature search, data collection, manuscript writing, and proofreading.
HS: Conception, manuscript writing, data analysis, interpretation of the results, and critical revision.
AS: Literature search, data collection, manuscript writing, and proofreading.
All authors approved the final version of the manuscript to be published.

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