Original Article

Role of Continuous Versus Alternate Regime of Thromboprophylaxis in Obstetric Outcome in Bad Obstetric History (BOH)

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Abstract

Objective: To compare the frequency of live births in patients with BOH taking LMWH daily versus alternate days.

Methods: This was a randomised controlled trial, conducted at the Department of Obstetrics and Gynaecology, at POF Hospital, Wah, from 1st of January to 31st of December 2024. This study included 122 women aged 30-45 years with a history of adverse obstetric outcomes. Participants were randomly assigned to receive 40 mg low molecular weight heparin (LMWH) either daily (Group A Control) or on alternate days (Group B Experimental) starting in first trimester at enrolment visit when fetal cardiac activity becomes positive, with follow-ups assessing compliance, symptoms, and fetal well-being through history and ultrasound. Live birth was the primary outcome. Data analysis was performed using SPSS v. 22, with p-values <0.05 considered statistically significant.

Results: The mean age was 34.90 ± 2.56 years, and the mean gestational age at enrolment was 9.95 ± 1.14 weeks. Among them, 46.7% underwent Spontaneous vaginal delivery, 39.3% Cesarean section, and 13.9% Evacuation and curettage, with 76.2% resulting in live births and 27.9% of newborns requiring Neonatal intensive care admission. No significant differences were observed between groups in terms of age, gestational age, mode of delivery, live birth frequency (p = 0.832), or Intrauterine death rates (p = 0.543). However, Neonatal intensive care unit admissions were significantly higher in the control group (p = 0.043).

Conclusion: The study found no significant difference between the two groups in terms of live births. However, neonatal intensive care unit admissions were significantly higher in the women receiving a daily low molecular weight heparin dose.

Keywords: Low-molecular-weight heparin, Bad obstetric History, Thromboprophylaxis, Pregnancy Outcome.

Contributions:
RM - Conception, Design
KA - Acquisition, Analysis, Interpretation
AN - Drafting
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Introduction

The most common symptoms of miscarriages are per vaginal bleeding and abdominal pain. Several factors may be responsible for miscarriages, like TORCH infections, cervical incompetence, uterine abnormalities like a bicornuate uterus, and lifestyle factors, e.g., alcohol. The causes of spontaneous miscarriages are multifactorial, involving interlinked genetic and non-genetic factors. Studies suggest that prior miscarriage history is the most critical factor in assessing the likelihood of recurrent pregnancy loss, while those with no prior miscarriages face substantially reduced chances of miscarriage in subsequent pregnancies.[1]

Recent studies have shown that thromboprophylaxis may help reduce the risk of miscarriage and improve live birth rates. A 2022 meta-analysis found that intravenous immunoglobulin could benefit older women with recurrent miscarriages, suggesting immunomodulation plays a role in managing recurrent pregnancy loss (RPL).[2] Additionally, progesterone, studied in 2020, has been shown to effectively prevent miscarriages, particularly in women with hormonal imbalances.[3] A meta-analysis including 1,452 participants found that LMWH lowers the risk of miscarriage in women who have had more than three miscarriages.[4] Research from 2019 involving 174 women with a history of RPL revealed that 85.4% achieved live births after LMWH therapy during pregnancy, confirming the treatment's effectiveness and safety in improving pregnancy success rates.

In 2022, a study in India explored the impact of thromboprophylaxis on recurrent pregnancy loss. It reported that term birth rates significantly increased when aspirin, enoxaparin, or progesterone was used in cases of unexplained recurrent pregnancy loss. Among 32 patients treated with enoxaparin, 29 (90.6%) had live births, 2 (6%) had miscarriages, and 1 (3.1%) experienced a stillbirth.[5]

Bremme et al assessed high-dose thromboprophylaxis in 47 high-risk pregnancies at Karolinska University Hospital. Dalteparin effectively prevented antenatal thrombosis with few maternal complications. Neonatal outcomes were poorer, especially in thrombophilic mothers.[6]

Due to the lack of literature on alternate dosing regimens of LMWH, a pilot study was conducted with 30 patients divided into two groups: Group A (alternate therapy) and Group B (daily therapy),

each with 15 patients. In Group A, 11 patients (73.3%) had live births, 2 (13.3%) had miscarriages, and 2 (13.3%) experienced preterm labour. In Group B, which received daily LMWH, 12 patients (80%) had live births, 3 (20%) had miscarriages, and no preterm labour was reportedWhile daily LMWH is commonly used in studies, there is little research comparing it with alternate-day thromboprophylaxis. This study examines the use of LMWH every other day as a new approach. Since alternate-day LMWH is more cost-effective than daily injections, this research could offer useful insights into treating recurrent miscarriages while balancing effectiveness and affordability.

Materials And Methods

This randomised controlled trial was conducted from 1st January 2024 to 30th June 2024 at the Obstetrics and Gynaecology department of POF Hospital, Wah. The Ethical approval was taken before conducting the study. The sample size of 122 (6l in each group) was calculated with a level of significance of 5%, power of test 80%, population proportion for the alternative group as is 73.3%[6] While for the daily group, as 90.6%.[5] The inclusion was defined as follows: women with a bad obstetrical history (BOH)and an age range of 30-45 years with gestational age of 8-12 weeks were enrolled in the study. The BOH was defined as a history of unexplained stillbirth or a history of 2 or more preterm labour and/or 3 or more consecutive miscarriages before 24 weeks of gestation. The women with 1 or 2 miscarriages and with comorbid conditions like heart disease, diabetes, hypertension and endocrine disorders were excluded from the study. The patients were randomly divided by computer-generated random numbers into group A and group B. In group A (control group), patients were given 40 mg LMWH daily, while in group B (experimental group), the same dose of LMWH was given on alternate days. Patients were followed fortnightly or admitted based on their history of bad obstetric outcomes and their level of compliance.

The contact details of all subjects were recorded, and they were informed about their scheduled visits in line with the study protocol. During each visit, diary records of taking low molecular weight heparin daily or on alternate days were checked. A detailed history was taken during each visit to assess symptoms of miscarriage, preterm labor, vaginal discharge, and vaginal spotting. Ultrasound examinations were performed at each visit to confirm viability, assess fetal growth parameters, and evaluate amniotic fluid index (AFI). For the mode of delivery at term, spontaneous labour was preferred unless the patient opted for induction of labour or elective lower-segment caesarean section (EL-LSCS). The outcome was measured in terms of live birth (delivery of a fetus with evidence of life).

The collected data were analysed using SPSS version 22. Qualitative variables, such as mode of delivery, parity, gravidity, mode of delivery, IUD, NICU admission and live birth, were measured in terms of frequency and percentages. Quantitative variables, such as patient age and gestational age, were measured in terms of mean and standard deviation. These groups were compared in terms of the frequency of live birth using Chi chi-squared test. Effect modifiers, such as age, gestational age, and mode of delivery, were stratified using a post-stratified chi-square test. A p-value of <0.05 was considered significant.

Results

The participants had an average age of 34.90 years (SD 2.56), with a mean gestational age of 9.95 weeks (SD 1.14) at the time of enrolment. Among the 122 women studied, 57 (46.7%) experienced spontaneous vaginal delivery (SVD), 48 (39.3%) underwent caesarean delivery (CSD), and 17 (13.9%) required evacuation and curettage (E&C). Adverse pregnancy outcomes included fetal loss in 17 cases (13.9%) and intrauterine death (IUD) in 12 cases (9.8%). Live births were documented in 93 patients (76.2%), with 34 newborns (27.9%) necessitating admission to the neonatal intensive care unit (NICU). No significant differences were observed between the groups regarding age distribution, gestational age, or mode of delivery (p = 0.755, p = 0.232, and p = 0.591, respectively; Table 1). Similarly, the mode of delivery did not differ between the groups (p = 0.591; Table 1).

Table 1: Comparison of Study Variables between Control and Experimental Group

Variables	Group A (Control group) (n=61)	Group B (Experimental group) (n=61)	Pearson Chi-square value	P value
Age (years)	34.98 ± 2.88	34.83 ± 2.30		0.755
Gestational age (weeks)	10.07 ± 1.23	9.83 ± 1.047		0.232
Mode of delivery				
SVD	26 (42.6%)	31 (50.8%)	1.051	0.591
CSD	25(41%)	23(37.7%)		
E&C	10(16.4%)	7(11.5%)		
Alive birth	46 (49.5%)	47 (50.5%)	0.45	0.832
IUD	5 (41.7%)	7 (58.3%)	0.370	0.543
NICU admission	22 (64.7%)	12 (35.3%)	4.078	0.043

Comparative analysis of outcomes revealed comparable rates of live births between group A (46 cases, 49.5%) and group B (47 cases, 50.5%; p = 0.832), with no significant variation in intrauterine death (IUD) frequency (p = 0.543). However, neonatal intensive care unit (NICU) admissions were significantly higher in the control group compared to the experimental group (p = 0.043; Table 1).

Stratified analysis further indicated that age, gestational age, and mode of delivery had no statistically significant influence on live birth rates ($p > 0.05$ for all variables.

Discussion

Pregnancy loss can have profound effects on women's mental health. While it is an irreversible event, its occurrence can be minimised through thorough risk assessment and preventive measures. The risk factors include the age of the mother, higher BMI and previous history of miscarriages.[1] Recurrent pregnancy loss poses a significant challenge in gynaecological practice, affecting approximately 2-4% of all pregnancies. In a subset of cases, the underlying cause remains unidentified. Unexplained recurrent pregnancy loss (URPL) is characterised by the sudden unplanned loss of three or more successive pregnancies without any identifiable risk factors. It accounts for approximately 40% to 50% of all cases of pregnancy loss. The wide use of Low molecular weight heparin (LMWH) in obstetric care, particularly for women with BOH, is well documented. The efficacy of LMWH is primarily attributed to its anticoagulant properties, which reduce the risk of thrombosis in placental circulation, a common pivotal pathological process in many cases of BOH.[5, 7] Low-dose prophylaxis with LMWH is effective in preventing metabolic and immunological disorders that contribute to placental inflammation, a key pathophysiological mechanism implicated in the development of various obstetrical complications.[8]

The mechanism of action of LMWH is due to its anticoagulant effects by inhibiting factor Xa and, to a lesser extent, thrombin, leading to a reduced risk of clot formation. In the context of BOH, which includes recurrent miscarriages, stillbirths, and severe intrauterine growth restriction (IUGR), thrombophilia disorders such as antiphospholipid syndrome (APS) and inherited thrombophilia are significant contributors. By improving placental blood flow and reducing microthrombi, LMWH enhances fetal and maternal outcomes. The frequency of administration plays a crucial role in maintaining therapeutic anticoagulation levels, directly impacting its efficacy. Low-molecular-weight heparin (LMWH) is effective in mitigating apoptotic cell death and oxidative toxicity in the thrombocytes of women with recurrent pregnancy loss (RPL). These protective effects appear to be linked to elevated intracellular calcium ion concentrations mediated by the activation of TRPM2 and TRPV1 channels.[9] The immunomodulation window gives some opportunity to use immunoglobulins in recurrent pregnancy losses.[2] Low molecular weight heparin (LMWH) enhances pregnancy outcomes by stimulating the proliferation and migration of stromal cells in early pregnancy and improving their decidualization. [10]

Daily administration of LMWH has been extensively studied in the literature and is considered the gold standard in managing thrombophilia-related BOH. The key advantages of daily dosing include consistent therapeutic levels, proven efficacy and a good safety profile.[11,12] The alternate-day regimen can be cost-effective with improved compliance and low risk of injection site problems.[6]Despite these advantages, alternate-day dosing has not been as extensively studied as daily administration. Concerns about suboptimal anticoagulation levels and increased risk of adverse outcomes remain significant limitations of this approach.

A pilot study involved enrolment of 30 subjects, who were evenly divided into two groups: Group A (alternate therapy) and Group B (daily therapy), with 15 subjects in each group. In Group A, which received alternate therapy, 11 subjects (73.3%) had live births, 2 subjects (13.3%) experienced miscarriages, and 2 subjects (13.3%) had preterm labour. Conversely, in Group B, where subjects were administered low LMWH daily, 12 subjects (80%) achieved live births, 3 subjects (20%) had miscarriages, and no cases of preterm labour were observed. The p-value based on these results is approximately 0.326, indicating no statistically significant difference in the distribution of live births, miscarriages, and preterm labour between the two groups.[6]In our study, comparative analysis of outcomes between groups revealed a similar frequency of live births, with 46 cases (49.5%) in Group A and 47 cases (50.5%) in Group B ($p= 0.832$). Furthermore, no significant difference was identified between the groups regarding the frequency of IUD (p-value: 0.543). However, NICU admissions were significantly higher in the control group compared to the experimental group (p-value: 0.043).

The decision between daily and alternate-day LMWH administration in the management of BOH involves a delicate balance between efficacy, safety, cost, and subjects' compliance. The regimen involving daily LMWH remains the standard of care; alternate-day dosing may be a reasonable alternative in selected subsets of subjects, particularly in low-resource settings. Further research is needed to establish guidelines for clinicians for the efficacy and safety of alternate-day regimens.

A systematic review and meta-analysis by Scarrone et al., which analysed six studies involving 1,016 participants, found no statistically significant improvement in live birth rates with low molecular weight heparin (LMWH) use in unexplained recurrent pregnancy loss (U-RPL). These findings contrast with earlier observational studies, such as one reporting an 85% live birth rate in LMWH-treated U-RPL patients versus 66% in untreated controls. However, the meta-analysis highlights persistent uncertainty in the evidence base, as conflicting results across trials—including variations in patient selection, LMWH dosing, and inclusion of heterogeneous populations (e.g., thrombophilia vs. idiopathic U-RPL)—may contribute to the lack of consensus.[13] Another meta-analysis showed that LMWH treatment may reduce the miscarriage rate in women with a history of ≥3 miscarriages.[4]

Akbari et al. conducted a randomised clinical trial involving 173 participants with a history of ≥2 unexplained early miscarriages. Participants were assigned to either LMWH combined with low-dose aspirin (Group A) or low-dose aspirin alone (Group B). The study found no statistically significant difference in live birth rates between groups (78% in Group A vs. 77.1% in Group B). While no major adverse events occurred, minor bleeding was reported in 18% of Group A participants.[14]

The administration of LMWH to pregnant women with thrombophilia may alter the multiples of the median (MoM) values of serum markers used in first- and second-trimester screening tests. While treatment with LMWH, obstetricians should be cognizant of this potential effect when recommending screening tests for subjects with thrombophilia and consider the option of fetal DNA testing as an alternative for this group.[15]

In women at high risk of developing preeclampsia without underlying thrombophilia, the combination of LMWH and low-dose aspirin (LDA) is more effective than LDA alone in preventing preeclampsia, preterm birth, and fetal growth restriction.[11,12] Another study was done to compare the efficacy of LMWH alone versus its combination with aspirin in the treatment of fetal growth restriction (FGR) in subjects. These findings suggested that the combination of LMWH with aspirin in FGR subjects effectively reduced maternal IL-6 and TNF-alpha levels, improved fetal development parameters, and decreased the incidence of pregnancy-related complications and adverse neonatal outcomes compared to LMWH treatment alone.[16-18]
The various formulations of LMWH are available, and there is considerable debate about the comparison of these forms. According to the data, enoxaparin demonstrated better efficacy among LMWHs in improving live birth rates (LBR) compared to controls, while also significantly lowering the incidence of pre-eclampsia, preterm delivery, and pregnancy loss. A dosage-based subgroup analysis indicated that both 20mg and 40mg doses of enoxaparin were associated with improved LBR, though the 20mg regimen demonstrated superior efficacy.[19] Another study found that fondaparinux has fewer side effects but similar outcomes compared to LMWH.[20]

Conclusions

This study found no significant impact of maternal age, gestational age, or mode of delivery on live birth outcomes. However, NICU admissions were significantly higher in the daily LMWH group, indicating differences in neonatal care requirements. Further research with a larger sample size is needed to explore factors influencing neonatal outcomes.

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