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Original Article

Effect of Early Enoxaparin Treatment on Fertility Outcomes in Assisted Reproductive Technology: A Randomized Clinical Trial

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Abstract

Background: This study aimed to evaluate whether early administration of enoxaparin could improve the success of assisted reproductive technology (ART), particularly by enhancing endometrial receptivity and embryo implantation. Enoxaparin, an anticoagulant, has been proposed to modulate uterine blood flow and inflammatory pathways, potentially leading to better ART outcomes.

Methods: In this randomized single-blind clinical trial, 90 infertile women undergoing IVF/ICSI were recruited and randomly assigned to two groups: an intervention group (n=45) receiving subcutaneous enoxaparin (1 mg/kg/day) starting three days before ART and continued until 14 days after embryo transfer, and a control group (n=45) receiving standard ART care. All analyses were conducted according to the intention-to-treat principle.

Results: The overall clinical pregnancy rate across all participants was 13.3%. In the intervention group, 15.6% achieved clinical pregnancy compared to 11.1% in the control group (RR: 1.40, 95% CI: 0.49–4.00; P=0.535), indicating no statistically significant difference. Biochemical pregnancy occurred in 33.3% of women receiving enoxaparin versus 20.0% in the control group (RR: 1.67, 95% CI: 0.82–3.39; P=0.153), which also did not reach statistical significance. Rates of miscarriage and ongoing pregnancy were similar between groups. Due to the short follow-up period, no live birth outcomes were recorded.

Conclusion: Early enoxaparin administration did not significantly improve ART success rates in this population. Based on these findings, routine use of enoxaparin as a primary or prophylactic adjunct in ART cycles is not supported.

Keywords: Infertility, Assisted reproductive technology, Enoxaparin, Clinical pregnancy, Drug treatment, Fertility rate

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Introduction

Infertility is a significant reproductive health issue affecting millions of couples worldwide. It is generally diagnosed when a couple fails to conceive after 12 months of regular, unprotected intercourse. Put simply, it implies that they have been unable to get pregnant even after trying for an entire year. However, for women who are ≥ 35 years old, infertility may be identified sooner (after just 6 months of unsuccessful attempts) because fertility naturally decreases with age.[1] In Iran, prevalence estimates range from 10% to 15%, indicating its importance as a public health concern.

According to the latest epidemiological research conducted in Iran, the infertility rate is between 10% and 15% among couples in the country, although some studies have reported rates as high as 20%. This number is particularly significant because it impacts approximately 3–4 million couples nationwide and carries substantial psychological and emotional effects (e.g., increased risk of divorce) for those involved.[2]

Assisted reproductive technology (ART), including in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), offers hope for many infertile couples. However, success rates remain modest, prompting investigation into adjuvant therapies in order to improve endometrial receptivity and implantation.[3,4] Consequently, adjunctive treatments aimed at enhancing endometrial receptivity and implantation are of great interest.

Enoxaparin, a low-molecular-weight heparin, is an anticoagulant with established use in preventing recurrent miscarriage, especially in women with thrombophilia.[5-7] Beyond its anticoagulant effects, enoxaparin may

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modulate inflammatory pathways and enhance uterine perfusion, potentially fostering a more receptive endometrium.[8-10] While some studies suggest benefit in ART for selected populations (e.g., thrombophilia), evidence for its prophylactic use in the general infertile population is inconsistent.[11-13] Specifically, the rationale for initiating enoxaparin several days prior to ART, to preemptively improve the endometrial milieu prior to embryo transfer, has not been well established in women without coagulation disorders.

Given the contradictory findings and lack of clear evidence supporting early prophylactic enoxaparin in unselected ART populations, this randomized clinical trial aims to evaluate the effect of early enoxaparin administration (starting three days before ART) on clinical pregnancy rates in infertile women undergoing IVF/ICSI at a single center.

Methods

Study Design and Participants

This parallel-group, randomized, single-blind (outcome assessor-blinded) clinical trial was conducted at Kamali Hospital, Karaj, Iran, in 2023. The study protocol was approved by the Ethics Committee of Alborz University of Medical Sciences (IR.ABZUMS.REC.1401.258) and registered in the Iranian Registry of Clinical Trials (IRCT20220530055028N1, registration date: January 30, 2023). Moreover, written informed consent was obtained from all participants before the study.

Inclusion Criteria: Women aged 20–40 years, infertility defined as failure to conceive after 1 year of regular unprotected intercourse (or 6 months if age ≥ 35), body mass index 18–30 kg/m², adequate ovarian reserve with suitable oocytes for fertilization, endometrial thickness > 7 mm, and planned IVF/ICSI cycle.

Exclusion Criteria: Any specific medical condition that could affect study outcomes (e.g., uncontrolled endocrine disorders or severe endometriosis), chronic use of enoxaparin prior to the study, known coagulation disorders (e.g., thrombophilia or platelet deficiency), history of previous miscarriage, or history of successful pregnancy.

Randomization and Blinding

Participants were randomly allocated to intervention or control groups (1:1) using block randomization (block size = 4) generated via STATA Version 18 software software (version) by an independent epidemiologist. Due to the intervention nature, participants and treating clinicians were not blinded. However, outcome assessors (gynecologists and laboratory personnel) were blinded to group allocation.

Intervention

All women underwent standard ovarian stimulation and IVF/ICSI protocols. In the intervention group, subcutaneous enoxaparin (Loparin, Iran Hormone Company) at a dose of 1 mg/kg/day was initiated three days before oocyte retrieval and continued until 14 days after embryo transfer. This dose was selected based on prior study in recurrent miscarriage to ensure adequate anticoagulant effect during the peri-implantation window. However, the control group received standard ART care without enoxaparin.[14]

Outcome Measures

Primary Outcome: Clinical pregnancy rate, defined as the presence of an intrauterine gestational sac on transvaginal ultrasound 4–6 weeks after embryo transfer.

Secondary Outcomes

Biochemical Pregnancy: Positive serum beta-human chorionic gonadotropin (β-hCG, ≥ 25 IU/L) 14 days post-transfer without subsequent ultrasound confirmation.

Miscarriage Rate: Loss of a clinically confirmed pregnancy before 20 weeks

Ongoing Pregnancy Rate: Clinical pregnancy without miscarriage at follow-up

Live Birth Rate: delivery of a live infant ≥ 24 weeks (not collected due to short follow-up).

Data Collection

Demographic, clinical, and cycle-specific data (age, body mass index, infertility duration, previous ART failures, smoking, parity, infertility type, follicle-stimulating hormone [FSH] dose, endometrial thickness, number of embryos transferred, embryo transfer day) were recorded, and outcomes were assessed via serum β-hCG tests and transvaginal ultrasound.

Statistical Analysis

Data were analyzed using SPSS, version 25. Descriptive statistics were reported as means ± standard deviations (SD), as well as frequencies and percentages for continuous and categorical variables, respectively. In addition, Mann–Whitney U and chi-square tests were used for group comparisons for continuous and categorical variables, respectively. The primary analysis followed intention-to-treat. Moreover, effect sizes were reported as relative risk (RR) with 95% confidence intervals (CIs) for binary outcomes. A *P*-value < 0.05 was considered statistically significant.

Sample Size

Using G*Power with an effect size of 0.25, a power of 80%, and an α of 0.05, a sample size of 45 per group (total 90) was determined to detect differences in clinical pregnancy rates. [10] The following formula was applied to calculate the sample size for comparing two independent proportions (the two groups):

$$n = \frac{((Z_{1-\alpha/2} + Z_{1-\beta})^2 \times (p_1(1 - p_1) + p_2(1 - p_2)))}{(p_1 - p_2)^2}$$

where

- $Z_{1-\alpha/2} = 1.96$ for 95% CI
- $Z_{1-\beta} = 0.84$ for 80% power
- p_1 and p_2 = expected proportions in the intervention and control groups, respectively
- $\alpha = 0.05$ (type I error)
- $\beta = 0.2$ (type II error)

Results

Between February and April 2023, 103 women were assessed for eligibility. Thirteen were excluded, and 90 were randomized (45 per group). All participants received the allocated intervention and completed the follow-up (Figure 1). Baseline demographic and clinical characteristics were well-balanced between the groups (Table 1). Additionally, parameters of the IVF cycle were similar (Table 2).

Primary Outcomes

Clinical pregnancy occurred in 12 women (13.3% of the total cohort): 7 (15.6%) in the intervention group and 5 (11.1%) in the control group (RR: 1.40, 95% CI: 0.49–4.00, $P = 0.535$, Table 3).

Secondary Outcomes

Biochemical pregnancy was observed in 15 women (33.3%) in the intervention group and 9 women (20.0%) in the control group (RR: 1.67, 95% CI: 0.82–3.39, $P = 0.153$). Among the 12 clinical pregnancies, miscarriage occurred

Table 1. Comparison of Baseline Demographic and Clinical Characteristics Between the Two Groups

Variable	Intervention Group (n = 45)	Control Group (n = 45)	*P* Value
Age (year)*	29.40 ± 2.87	29.00 ± 4.02	0.316
BMI (kg/m²)*	23.21 ± 2.10	23.36 ± 2.69	0.805
Duration of infertility (year)*	3.29 ± 2.43	3.27 ± 1.69	0.478
Number of previous unsuccessful ART cycles*	2.76 ± 1.30	2.80 ± 1.30	0.707
Smoking status**	13 (48.1%)	14 (51.9%)	0.818
Nulliparity**	38 (51.4%)	36 (48.6%)	0.581
Primary infertility**	35 (52.2%)	32 (47.8%)	0.468

Note. *Data are presented as means ± standard deviation, Mann-Whitney U test. **Data are presented as n (%), Chi-square test. BMI: Body mass index; ART: Assisted reproductive technology.

Table 2. Comparison of IVF Cycle Characteristics Between the Two Study Groups

Variables	Intervention Group	Control Group	*P* Value
FSH dose (IU)	3148.60 ± 1212.12	3086.02 ± 1229.02	0.713
Endometrial thickness stimulation time	8.87 ± 1.80	9.53 ± 1.89	0.147
Number of embryos transferred	2.31 ± 1.10	2.31 ± 1.10	0.999
Embryo transfer date	3.47 ± 0.89	3.49 ± 0.99	0.981

Note. Data presented as means ± standard deviation. IVF: In vitro fertilization; Mann–Whitney U test. FSH: Follicle-stimulating hormone.

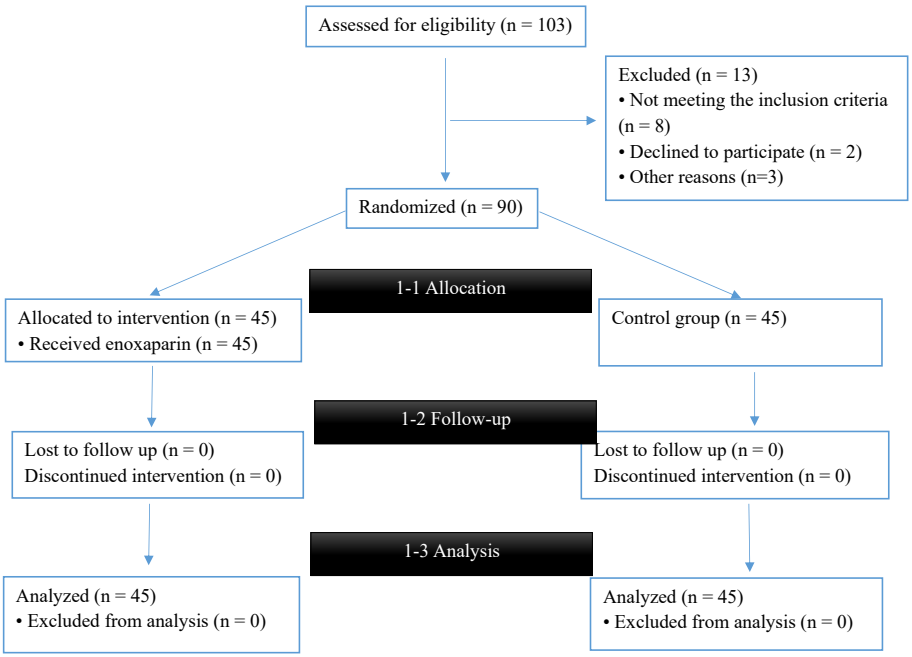

Figure 1. Consort Flowchart

Table 3. Comparison of Fertility and Pregnancy Outcomes Between the Two Groups

Outcome	Intervention Group	Control Group	*P* Value
Clinical pregnancy	7 (58.3%)	5 (41.7%)	0.535
Miscarriage	3 (42.9%)	4 (57.1%)	0.694
Pregnancy without miscarriage	4 (66.7%)	2 (33.3%)	0.414
Biochemical pregnancy	15 (62.5%)	9 (20.0%)	0.153

Note. Data are presented as n (%). Chi-square test.

in 3 women (42.9%) in the intervention group and 4 women (57.1%) in the control group ($P=0.694$), resulting in 4 (8.9%) and 2 (4.4%) ongoing pregnancies, respectively ($P=0.414$). It should be noted that live birth data were not collected due to the short follow-up period.

Discussion

This randomized clinical trial investigated the effect of early enoxaparin administration on fertility outcomes in women undergoing ART. The main findings indicated that while the number of clinical pregnancy, biochemical pregnancy, and pregnancy without miscarriage was high in the enoxaparin group compared to the control group, none of these differences reached statistical significance.

Our findings are consistent with those of some studies conducted in general ART populations,[15] but contradict the results of other studies, reporting benefit in selected groups, such as women with thrombophilia or recurrent implantation failure.[6,16] This discrepancy likely reflects differences in patient characteristics, suggesting that any potential benefit of anticoagulant therapy may be confined to high-risk subgroups rather than the general infertile population.

Nonetheless, Sacks and Zhang concluded that the use of prednisolone and enoxaparin may improve the success rate of IVF,[17] which corroborates our findings. Moreover, Grandone et al reported that the use of enoxaparin was slightly associated with greater success and fertility.[18] Likewise, the findings of the study by Bates demonstrated that prophylactic use of anticoagulants in women with thrombophilia disorders is related to improved success rates in ART,[19] which contradicts the results of the present study. This discrepancy may be attributed to differences in the study populations. One study focused on women with diagnosed thrombophilic conditions, and the current study included women with no underlying coagulation abnormalities, suggesting that the potential benefits of anticoagulant therapy may be limited to high-risk groups rather than the general population of infertile women undergoing ART.

There was no significant difference in the correlation between any of the demographic characteristics, implying that there was no difference between the two intervention and control groups in terms of baseline characteristics. Additionally, in examining the cycle characteristics of the studied women, no significant differences were found in the dose of FSH, endometrial thickness at the time of stimulation, number of embryos transferred, and day of embryo transfer between the two groups, and both groups were similar in terms of ART ($P>0.05$). Our findings confirmed that FSH can be affected by certain interventions, such as lifestyle changes or herbal extracts.[20,21] Moreover, the effects of heparin on FSH levels had been confirmed in a study.[16] However, the results of the present study showed that this hormone may not be affected by anticoagulant treatments, such as enoxaparin. Overall, these results suggest that improvements in fertility outcomes may occur through different biological pathways and that changes in FSH levels are not always a necessary factor.

Our data further revealed a total clinical pregnancy rate of 13.3%, with no statistically significant difference between the intervention group receiving enoxaparin (58.3%) and the control group (41.7%). Similarly, while there was a trend toward lower miscarriage rates in the enoxaparin group, the difference was not statistically significant ($P>0.005$). Based on the results, while enoxaparin was associated with an increased rate of biochemical pregnancies, 15 cases (62.5%) in the intervention group compared to 9 cases (20.0%) in the control group, this difference was not statistically significant ($P=0.153$). This issue represents that although enoxaparin may have some influence on early implantation as indicated by elevated β-hCG levels, it does not lead to a meaningful or statistically supported improvement in pregnancy outcomes. Therefore, the findings indicate that enoxaparin, when used as an adjuvant in ART for the general population of infertile women without coagulation disorders, does not significantly enhance the likelihood of successful fertility outcomes.

Study Limitations

Key limitations included the short follow-up, precluding assessment of live birth, a critical ART outcome. Moreover, the single-center design and relatively small sample may limit generalizability. Although randomization ensured group comparability, residual confounding could not be entirely excluded. Additionally, the use of a weight-based therapeutic dose rather than a fixed low prophylactic dose may influence the results and requires further study.

Conclusion

Early enoxaparin administration failed to significantly enhance ART success rates in infertile women without coagulation disorders. Accordingly, routine prophylactic use is not recommended in this population. Future studies with larger cohorts, longer follow-up, and targeted inclusion of high-risk subgroups are warranted to further investigate this issue.

Ethics statement

This study was approved by Research Ethics Committees of Alborz University of Medical Sciences. Ethical code:IR.ABZUMS.REC.1401.258.

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Conflict of interests declaration
There is no conflict of interests in relation to the publication of this article.

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Data availability statement
Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Consent for publication
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