Original Article
Effect of low-molecular-weight heparin on gestational sac and embryo development, and miscarriage prevention for recurrent spontaneous abortion

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Abstract: Objective: To evaluate the efficacy of low-molecular-weight heparin (LMWH) in pregnant women with recurrent spontaneous abortion (RSA) and to investigate the correlation with changes in the gestational sac and embryo development, and miscarriage prevention as outcomes. Methods: A retrospective analysis was conducted on 100 pregnant women with RSA treated at Hulunbeier People's Hospital between January 2022 and January 2023. Among them, 52 patients received LMWH therapy (observation group), while 48 received routine treatment (control group). Serum levels of human chorionic gonadotropin (hCG), progesterone (P), estradiol (E2), and coagulation markers (D-dimer [D-D], plasminogen activator inhibitor 1 [PAI-1], and fibrinogen), as well as gestational sac diameter (GSD), embryo length (EL), and uterine artery blood flow resistance, were assessed before and after treatment. Pregnancy outcome and adverse reaction rate were recorded and compared. Patients were categorized into successful and unsuccessful groups based on miscarriage prevention outcomes, and differences in GSD and EL were analyzed. Logistic regression was performed to identify factors influencing miscarriage prevention. Results: Baseline hCG, P, E2, D-D, PAI-1, fibrinogen, GSD, EL, and uterine artery blood flow resistance were comparable between groups (all P>0.05). After treatment, these measuremnts improved significantly, with greater changes in the observation group (all P<0.05). The term pregnancy rate was significantly higher in the observation group than in the control group (P<0.05), while adverse reaction rates were similar (P>0.05). The successful group exhibited significantly greater GSD and EL compared to the unsuccessful group (P<0.05). Logistic regression identified age, number of miscarriages, and LMWH use as independent factors influencing miscarriage prevention outcome (P<0.05). Conclusions: LMWH therapy significantly improves hormone levels, coagulation status, GSD, and EL in pregnant women with RSA, enhancing miscarriage prevention outcomes with minimal adverse reactions, making it a safe and effective treatment option for clinical practice.

Keywords: Recurrent spontaneous abortion, low-molecular-weight heparin, gestational sac, embryo, miscarriage prevention outcomes

Introduction

Recurrent spontaneous abortion (RSA) is a prevalent condition in obstetrics and gynecology, with an incidence of approximately 4% among women of childbearing age. A history of spontaneous abortion is recognized as an independent risk factor for RSA. The incidence of clinical spontaneous abortion is 15%-25%, with 80% occurring as early abortions before 12 weeks of gestation [1, 2]. RSA is a multifactorial condition characterized by complex pathogenesis and nonspecific symptoms. Key contributing factors include low progesterone (P) levels, chromosomal abnormalities, cervical incompetence, reproductive system infections, and uterine microthrombosis. RSA severely harms patients' physical and mental health, as well as family well-being, and clinical treatments are often suboptimal [3].

Anticoagulation therapy has demonstrated efficacy in managing RSA. Among anticoagulants, low-molecular-weight heparin (LMWH) sodium plays a critical role by reducing blood viscosity, preventing thrombosis, promoting thromboly-

sis, and increasing placental blood flow [4]. LMWH also has anti-inflammatory effects, modulating the complement and immune systems, inhibiting excessive complement activation, enhancing trophoblast proliferation and invasion, improving fetoplacental microcirculation, and increasing uteroplacental perfusion, thereby reducing RSA incidence [5, 6].

The outcome of RSA is influenced not only by placental microcirculation but also by the condition of the gestational sac and embryo. The gestational sac serves as the structure for embryonic development within the uterus, while the embryo resides within the sac [7]. Studies have shown that the size, morphology, and development of the gestational sac and embryo are closely associated with miscarriage prevention outcome in early threatened abortion [8].

A review of RSA cases treated with LMWH sodium suggested that this therapy may improve gestational sac and embryo conditions, leading to better miscarriage prevention outcomes. Although LMWH sodium has shown promising results in RSA patients with prethrombotic status, few studies have explored its effect on gestational sac and embryo changes and their correlation with miscarriage prevention outcomes.

Materials and methods

Clinical data

This retrospective study analyzed 100 RSA cases treated at Hulunbeier People's Hospital from January 2022 to January 2023. Among them, 52 patients treated with LMWH formed the observation group, while 48 patients receiving routine treatment constituted the control group.

Inclusion criteria: ① Patients with at least two previous spontaneous abortions (including biochemical pregnancies and embryo arrests) meeting RSA diagnostic criteria [9]. ② Normal karyotypes of both partners. ③ Complete clinical data.

Exclusion criteria: ① History of cesarean section or significant intrauterine manipulation. ② Reproductive organ abnormalities (e.g., uter-ine malformations, fibroids, cervical incompetence). ③ Severe liver or kidney dysfunction or malignancy. ④ Other infectious or autoimmune diseases.

Treatment methods

All patients received routine hormonal therapy for miscarriage prevention following a positive urine or blood test for human chorionic gonadotropin (hCG). Dydrogesterone was administered orally at an initial dose of 40 mg, followed by 10 mg every 8 hours. Additionally, 40 mg of progesterone was injected intramuscularly twice daily. Patients were advised to maintain bed rest and consume a nutritious diet.

In the observation group, LMWH (GlaxoSmithKline Tianjin Co., Ltd.) was administered at a dose of 4100 IU once daily in addition to routine treatment. All patients received treatment for two weeks.

Outcome measures

Fasting venous blood samples were collected from patients and centrifuged to obtain the supernatant. Serum levels of hCG, P, and estradiol (E2) were measured using electrochemiluminescence immunoassay.

Coagulation markers, including D-dimer (D-D), plasminogen activator inhibitor 1 (PAI-1), and fibrinogen, were quantified using an automatic biochemical analyzer before and after treatment for comparative analysis.

Gestational sac diameter (GSD) and embryo length (EL) were measured by B-ultrasound before and after treatment.

After routine abdominal ultrasound, Doppler ultrasound was used to measure transvaginal blood flow parameters of the cervical and uterine arteries. Using a probe frequency of 3.5-5.0 MHz, the average of three measurements was recorded. Parameters included the systolic/diastolic velocity ratio (S/D), pulsatility index (PI), and resistance index (RI) of the artery at the end of contraction.

Pregnancy outcomes, including term pregnancy, premature birth, and miscarriage, were recorded and compared between the groups.

Table 1. Comparison of general data

Factor	Observation group (n=52)	Control group (n=48)	t/χ^2	P
Age (years)			0.000	0.987
≥26	27 (51.92)	25 (52.08)		
<26	25 (48.08)	23 (47.92)		
Body mass index (kg/m^2)			0.001	0.974
≥23	28 (53.85)	26 (54.17)		
<23	24 (46.15)	22 (45.83)		
Number of miscarriages			0.107	0.744
2 times	20 (38.46)	20 (41.67)		
>2 times	32 (61.54)	28 (58.33)		
Gestational week	11.04±1.17	11.13±1.18	0.383	0.703
Duration of vaginal bleeding (d)			0.000	0.987
≤3	27 (51.92)	25 (52.08)		
>3	25 (48.08)	23 (47.92)		

Adverse reactions, such as gastrointestinal disturbances, rashes, gingival bleeding, and ecchymosis, were documented and compared.

Patients were divided into successful and unsuccessful groups based on pregnancy outcomes to compare GSD and EL changes between the groups.

Statistical methods

Data analysis was performed using SPSS 20.0, and visualizations were created using GraphPad Prism 8. Sample size calculation was based on N=Z2×(P×(1-P))/E2, where Z is the statistic (z=1.64 at 90% confidence), E is the error value, and P is the probability value. Independent sample t-tests were employed for inter-group comparisons, and paired t-tests were used for intra-group analyses of measured data. Chi-square tests were applied to analyze categorical data. A significance level of P<0.05 was considered significant.

Results

Comparison of general information

The observation and control groups were comparable in terms of age, body mass index, number of miscarriages, and other baseline characteristics (all P>0.05; **Table 1**).

Comparison of hormonal levels

No significant inter-group differences in P, E2, or hCG levels were observed before treatment (P>0.05). After treatment, these levels signifi-

cantly increased in both groups, with more pronounced elevations in the observation group compared to the control group (all P<0.05; **Figure 1**).

Comparison of coagulation function indexes

Baseline levels of D-D, PAI-1, and fibrinogen showed no significant differences between groups (all P>0.05). Post-treatment levels decreased significantly in both groups, with greater reductions in the observation group (all P<0.05; **Figure 2**).

Comparison of GSD and EL

Pre-treatment GSD and EL values were similar between groups (both P>0.05). Post-treatment, both values increased significantly in both groups, with greater increases observed in the observation group (both P<0.05; **Figure 3**).

Comparison of uterine artery blood flow resistance before and after treatment

The arterial blood flow resistance parameters S/D, PI, and RI were significantly higher in both the observation and control groups compared to normal values before treatment (P<0.05). After treatment, these values decreased in both groups, with the observation group showing greater reductions than the control group (all P<0.05; **Figure 4**).

Comparison of pregnancy outcomes

The premature birth rate, miscarriage rate, and term pregnancy rate were 7.69%, 9.62%, and
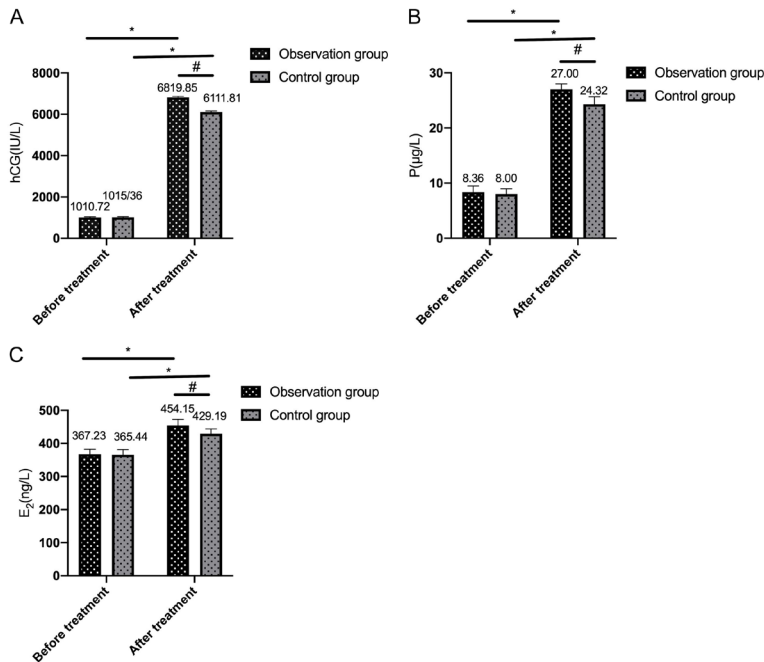
Figure 1. Comparison of progesterone levels. A: Comparison of human chorionic gonadotropin (hCG) levels between the two groups before and after treatment; B: Comparison of progesterone (P) levels between the two groups before and after treatment; C: Comparison of estradiol (E_2) levels between the two groups before and after treatment. Note: * denotes P<0.05 in the intra-group comparison before and after treatment; # denotes P<0.05 in the inter-group comparison after treatment.

Figure 2. Comparison of coagulation function. A: Comparison of D-dimer (D-D) between the two groups before and after treatment; B: Comparison of plasminogen activator inhibitor 1 (PAI-1) between the two groups before and after treatment; C: Comparison of fibrinogen between the two groups before and after treatment. Note: * denotes P<0.05 in the intra-group comparison before and after treatment; # denotes P<0.05 in the inter-group comparison after treatment.
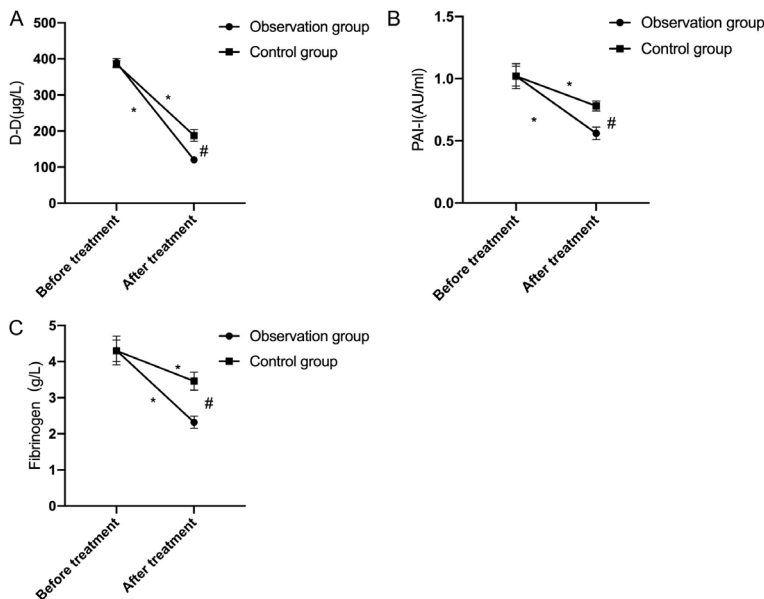
82.69% in the observation group, respectively, compared to 16.67%, 27.07%, and 56.25% in the control group. The observation group had a significantly lower miscarriage rate and a higher term pregnancy rate than the control group (both P<0.05; **Table 2**).

Comparison of adverse reactions

In the observation group, 3 patients experienced gastrointestinal reactions, 1 had a rash, 1 had gingival bleeding, and 1 had ecchymosis, resulting in an overall incidence of 11.54%. In the control group, 3 patients experienced gastrointestinal reactions, 2 had rashes, 1 had gingival bleeding, and 1 had ecchymosis, with a total incidence of 14.58%. The difference in adverse reaction rate between the two groups was not significant (P>0.05; **Table 3**).

Comparison of GSD and EL in patients with different miscarriage prevention outcomes

Based on treatment outcome, patients were divided into two groups: 70 cases with successful miscarriage prevention and 30 cases with unsuccessful outcome. Patients in the successful group had significantly longer GSD and EL compared to those in the unsuccessful group (both P< 0.05; **Table 4**).

Comparison of clinical characteristics of patients with different miscarriage prevention outcomes

To further investigate factors influencing miscarriage prevention outcome, clinical characteristics were analyzed
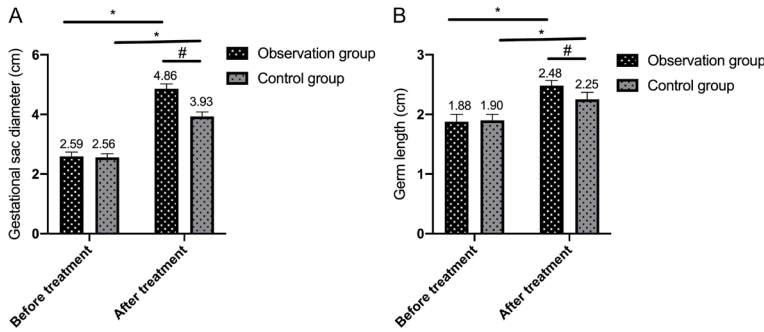
Figure 3. Comparison of gestational sac diameter and embryo length. A: Comparison of gestational sac diameter between the two groups before and after treatment; B: Comparison of embryo length between the two groups before and after treatment. Note: * denotes P<0.05 in the intra-group comparison before and after treatment; # denotes P<0.05 in the inter-group comparison after treatment.

(**Table 5**). Univariate analysis revealed that age, number of miscarriages, and heparin use were associated with miscarriage prevention. Multivariate logistic regression confirmed these variables as independent factors affecting miscarriage prevention (**Table 6**).

Discussion

In recent years, the incidence of RSA has been increasing, affecting 1%-3% of women of childbearing age [10]. RSA is characterized by a complex etiology, with endogenous P deficiency being one of the primary causes. Current clinical treatments often involve bed rest and P supplementation [11]; however, improving miscarriage prevention outcome remains a significant clinical challenge.

Dydrogesterone, a natural progesterone analog, binds to P receptors to exert progestational effects by inhibiting uterine contractions and improving the uterine environment to support embryo implantation. Additionally, it enhances nitric oxide synthesis in placental blood vessel walls, dilates microvessels, and increases uterine blood flow, making it a common treatment for threatened abortion [12]. LMWH, known for its strong anticoagulant effect through selective inhibition of coagulation factor X and its minimal impact on coagulation factor II, offers high safety [13]. LMWH effectively prevents thrombosis, improves local microcirculation, promotes blastocyst adhesion and endometrial invasion, stimulates trophoblast proliferation, enhances placental microcirculation, and shields embryos from mater-
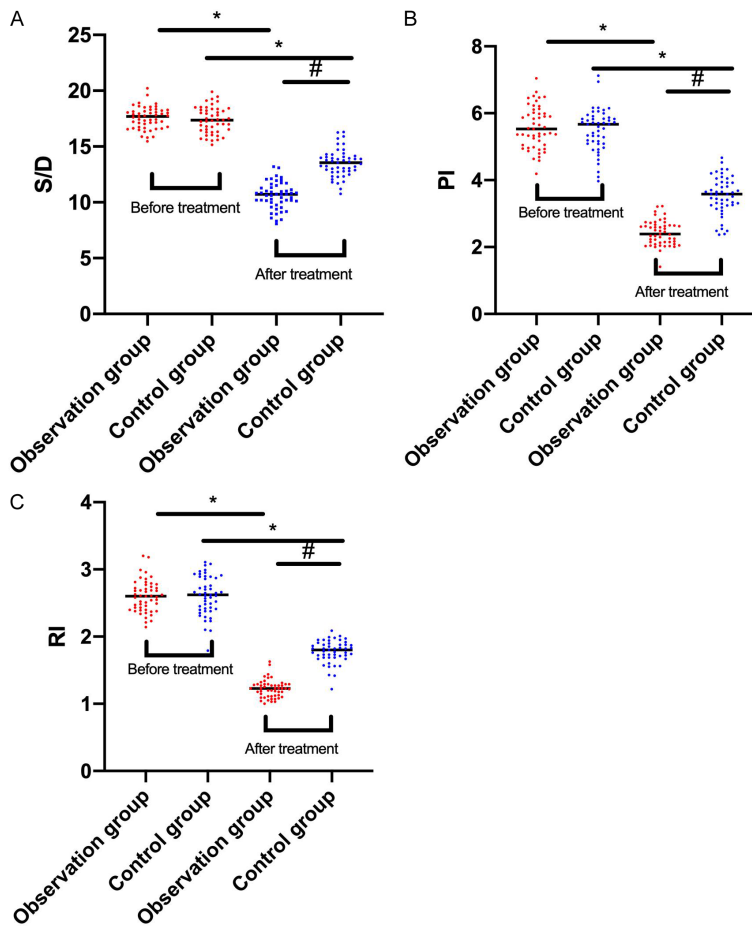

Figure 4. Comparison of uterine artery blood flow resistance before and after treatment between the two groups of patients. A: Comparison of peak/end-diastolic velocity value (S/D) between the two groups of patients before and after treatment; B: Comparison of pulsatility index (PI) between the two groups of patients before and after treatment; C: Comparison of resistance index (RI) between the two groups of patients before and after treatment. Note: * indicates that P<0.05 in comparing between the two groups of patients before and after treatment, and # indicates that P<0.05 in comparing between the two groups of patients after treatment.

Table 2. Comparison of pregnancy outcomes

Category	Observation group (n=52)	Control group (n=48)	χ^2	P
Premature birth rate	4 (7.69)	8 (16.67)	1.904	0.167
Miscarriage rate	5 (9.62)	13 (27.08)	5.160	0.023
Term pregnancy rate	43 (82.69)	27 (56.25)	8.310	0.004

Table 3. Comparison of adverse reactions [n, (%)]

Adverse reaction	Observation group n=52	Control group n=48	χ^2	P
Gastrointestinal reactions	3 (5.77)	3 (6.25)	-	-
Rashes	1 (1.92)	2 (4.17)	-	-
Gingival bleeding	1 (1.92)	1 (2.08)	-	-
Ecchymosis	1 (1.92)	1 (2.08)	-	-
Incidence of adverse reactions	6 (11.54)	7 (14.58)	0.205	0.651

Table 4. Comparison of gestational sac diameter and embryo length in patients with different miscarriage prevention outcomes

Category	Successful group n=70	Unsuccessful group n=30	t	P
Gestational sac diameter	4.54±0.47	4.13±0.41	4.147	<0.001
Embryo length	2.43±0.12	2.23±0.14	7.260	<0.001

nal immune attacks, thereby reducing the incidence of RSA [14].

This study evaluated the effects of LMWH in RSA patients. Our findings revealed that the observation group demonstrated significantly greater improvement in serum hormone levels compared to the control group. hCG maintains luteal function [15]. P is essential for conception and pregnancy maintenance [16], and E2 supports intrauterine growth and development [17]. These results suggest that LMWH enhances P and estrogen levels, benefiting fetal growth. Previous studies [18] have shown that LMWH promotes trophoblast proliferation, enhances invasiveness, and increases hCG secretion. However, its impact on E2 and P remained unconfirmed.

We hypothesize that the improved hormone levels observed in this study are influenced by concurrent hormone therapy. Nonetheless, the mechanisms underlying the more pronounced improvement in the observation group compared to the control group warrant further investigation.

We compared coagulation function between the two groups. Serum D-D, PAI-1, and fibrino-gen levels significantly decreased in patients receiving LMWH compared to those receiving routine treatment. D-D is a specific product of fibrinolytic enzyme activity and serves as a serum marker for hypercoagulability and fibrinolysis [19]. PAI-1 reflects the body's thrombotic tendency, with elevated levels promoting local thrombosis formation and progression [20]. Fibrinogen contributes to platelet aggregation, increased blood viscosity, and vascular endothelial injury, thereby enhancing erythrocyte adhesion and thrombosis [21]. These findings suggest that LMWH alleviates hypercoagulability, prevents thrombosis, and maintains blood supply to the uterus and placenta.

Subsequently, GSD, EL, and pregnancy outcomes were assessed. The observation group demonstrated significantly greater GSD and EL, along with a higher term pregnancy rate than the control group. These findings indicate that LMWH therapy improves GSD and EL, enhancing pregnancy outcomes. The gestational sac, characterized by the "double decidual sac sign", is a key marker for diagnosing intrauterine pregnancy before the yolk sac becomes visible [22]. Studies have shown that a gestational sac diameter >20 mm without an

Table 5. Univariate analysis

Factor	Successful group n=70	Unsuccessful group n=30	χ^2	P
Age (years)			8.310	0.004
≤26 (n=52)	43 (61.43)	9 (30.00)		
>26 (n=48)	27 (38.57)	21 (70.00)		
Body mass index (kg/m^2)			0.928	0.335
≥23 (n=54)	40 (57.14)	14 (46.67)		
<23 (n=46)	30 (42.86)	16 (53.33)		
Number of miscarriages (times)			16.07	<0.001
≤2 (n=40)	37 (52.86)	3 (10.00)		
>2 (n=60)	33 (47.14)	27 (90.00)		
Duration of vaginal bleeding (d)			0.374	0.541
≤3 (n=52)	35 (50.00)	17 (56.67)		
>3 (n=48)	35 (50.00)	13 (43.33)		
Use of low-molecular-weight heparin			14.11	<0.001
With (n=52)	45 (64.29)	7 (23.33)		
Without (n=48)	25 (35.71)	23 (76.67)		

Table 6. Multivariate analysis

Factor	B	S.E.	Wals	P	Exp (B)	95% C.I. Lower bound	Upper bound
Age	1.723	0.594	8.408	0.004	5.600	1.748	17.945
Body mass index (kg/m^2)	0.649	0.576	1.270	0.261	1.913	0.619	5.912
Number of miscarriages	2.547	0.738	11.905	0.001	12.775	3.005	54.301
Duration of vaginal bleeding	-0.523	0.563	0.862	0.353	0.593	0.197	1.787
Use of low-molecular-weight heparin	1.634	0.581	7.916	0.005	5.123	1.642	15.988

embryo suggests an empty sac. At 5 weeks of pregnancy, the yolk sac is the first anatomic structure within the gestational sac that ultrasound can detect. It serves, as a hallmark of intrauterine pregnancy [22]. Yolk sac diameters >10 mm or <3 mm are associated with poor pregnancy outcomes [23]. These findings highlight the strong correlation between GSD, EL, and pregnancy outcome.

We further analyzed GSD and EL in the successful and unsuccessful groups. Patients in the successful group had significantly greater GSD and EL, indicating that these metrics are closely associated with miscarriage prevention outcomes and can serve as indicators for evaluating the effectiveness of LMWH therapy in RSA patients.

Analysis of adverse reactions showed no significant difference between the groups, confirming that LMWH is safe for RSA treatment. Previous studies [24] have demonstrated the favorable anticoagulant effects of LMWH and its low bleeding risk, consistent with our findings.

In conclusion, LMWH therapy significantly improves hormone levels, coagulation status, GSD, and EL in pregnant women with RSA, leading to better miscarriage prevention outcomes. The treatment is associated with minimal adverse reactions and high safety, making it a valuable option for clinical practice.

Disclosure of conflict of interest

None.

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