Comparison of doses of heparin for venous thromboembolism and bleeding in pregnant women

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ABSTRACT

The evaluation criteria for dosage of low-molecular-weight heparin (LMWH) for pregnant women at high risk of venous thromboembolism (VTE) remain unclear. A retrospective study was performed to investigate the relative appropriate LMWH administration strategy and dosage for pregnant women at risk of VTE. 219 pregnant women with perinatal and postpartum VTE were reviewed and divided into group A (fixed dose group: n=73, 5000 IU dalteparin daily for all women), group B (weight group: n=73, 2500 IU dalteparin daily for women less than 50 kg; 5000 IU dalteparin daily for women more than 50 kg), and group C (anti-factor Xa (FXa) + weight group: n=73, 5000 IU once daily for women less than 50 kg; 7500 IU once daily for women weighing 50–80 kg; 10,000 IU once daily for women weighing over 80 kg). Further dose administration was adjusted according to peak anti-FXa level, maintaining the peak at the 0.5–1.0 IU/mL range. Women in group C presented lower incidence of VTE and other pregnancy complications than group A and group B. Adjusting the dosage of LMWH according to both weight and anti-FXa level of pregnant women not only prevented VTE but also reduced the risk of postpartum hemorrhage induced by LMWH administration. In addition, adjusting the dose of LMWH according to anti-FXa level and body weight also affected the recurrence of VTE and the occurrence of postpartum hemorrhage in pregnant women.

Significance of this study

What is already known about this subject?

► The evaluation criteria for dosage of low-molecular-weight heparin (LMWH) for pregnant women at high risk of venous thromboembolism (VTE) remain unclear.

What are the new findings?

► Women in group C presented lower incidence of VTE and other pregnancy complications than group A and group B.

► Adjusting the dosage of LMWH according to both weight and anti-factor Xa level of pregnant women not only prevented VTE but also reduced the risk of postpartum hemorrhage induced by LMWH administration.

How might these results change the focus of research or clinical practice?

► Current studies are rather limited and more comprehensive clinical trials need to be done to confirm their findings.

INTRODUCTION

Obstetrics-related venous thromboembolism (VTE) has been listed as one of the most fatal and common pregnancy complications. It is estimated to account for 9.3% of maternal morbidity and mortality in the USA from 2006 to 2008.[1–3] Due to acquired pregnancy thrombosis and its possible development into pulmonary embolism (PE) or deep vein thrombosis (DVT), the perinatal and postpartum maternal mortality caused by VTE is more than five times higher than other complications such as hydatidiform mole, miscarriage, and premature delivery.[4 5] Therefore, it is urgent to identify a more efficient strategy for prophylaxis and management of VTE.

The deceptive and atypical initial symptoms of VTE, such as hyperemia, dyspnea, limb edema, or bulb pain, are common in pregnancy and puerperium, which therefore often lead to uncertain diagnosis and delayed treatment.[6–8] Moreover, women with a history of VTE are around 2–10 times more likely to suffer from VTE than non-pregnant women.[9] To prevent the recurrence of VTE, low-molecular-weight heparin (LMWH) with a fixed prophylactic and intermediate dose has been recommended as pregnancy and postpartum thromboprophylaxis by the American College of Chest Physicians (ACCP) guidelines.[10 11] Accumulating evidence has demonstrated that incorrect usage of anticoagulant drugs increases the risk of severe bleeding and recurrence of thromboembolism.[12–14] An evaluating strategy should be established to adjust the dose of LMWH precisely for patients at high risk of VTE.

Among all the factors, alterations in anti-factor Xa (FXa) level and body weight play crucial roles in the pharmacodynamics and pharmacokinetics of LMWH in pregnant women at high risk of VTE.[15] It has been reported

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that anti-FXa in the serum functions as a biomarker to evaluate the satisfactoriness of thromboprophylaxis in patients.[16 17] However, current studies are rather limited and more comprehensive clinical trials need to be done to confirm their findings.

MATERIALS AND METHODS

Participants and procedure

From 2015 to 2018, pregnant women at higher risk of VTE at Tianjin First Center Hospital were reviewed in order to demonstrate that correcting the dosage of LMWH based on anti-FXa level and weight synchronously and significantly reduced the frequency of VTE in women with thrombophilia. All patients participating in the study had signed informed consent. The inclusion criteria and exclusion criteria are presented in online supplemental table S1.

Intervention

There were three groups in the study, with 73 participants per group. The experimental procedure can be found in online supplemental figure S1. Women in the control group (group A) were given a fixed dose (5000 IU) of dalteparin once daily until delivery despite variations in their weight and anti-FXa level. Pregnant women in the weight group (group B) were given a dosage of dalteparin according to their weight: those weighing less than 50 kg were given 2500 IU dalteparin once a day, those weighing between 50 kg and 80 kg were given 5000 IU dalteparin per day, and those weighing over 80 kg were given 7500 IU dalteparin per day. Women in the anti-FXa and weight group (group C) were given a dosage of dalteparin according to the anti-FXa level as well as body weight. Initially, dose administration of dalteparin was given according to body weight in the following manner: 5000 IU once daily for women weighing less than 50 kg; 7500 IU once daily for women weighing 50–80 kg; and 10,000 IU once daily for women weighing over 80 kg. Further dose administration was adjusted according to the peak anti-FXa level, maintaining the peak (2 hours after dosing) in the 0.5–1.0 IU/mL range. Blood samples were obtained from all women at 2 and 4 hours after each injection. The level of anti-FXa was examined by an automatic fluorescence analysis kit (American Type Culture Collection, Manassas, Virginia, USA) and the corresponding LMWH level was then calculated by the IL Coagulator System (Invitrogen Life Technologies, Carlsbad, California, USA). Blood samples of women in this group were collected and tested every 6 hours after injection and the computer system then calculated the dosage of dalteparin for the next injection. In addition, all tests were performed by professionally trained personnel at Tianjin First Center Hospital to maintain consistency in test results.

We stopped giving medication to pregnant women before delivery, 24 hours ahead of schedule. LMWH administration was resumed within 12–24 hours after delivery. All prenatal and postnatal care of pregnant women were performed according to standards, except for drug administration and dosage. All pregnant women received daily injections at the same time in a blind fashion. Participants in group A and group B were given saline injections.

Primary outcomes

The primary outcomes were the preventive effects of various modes of administration against VTE. Anti-factor Xa levels were recorded and stratified into therapeutic (<0.6), subtherapeutic (0.6–1.0), or supratherapeutic (>1.0). The fraction of women within each level was compared at three timepoints (antepartum, 1 week post partum, and 6 weeks post partum). Early recurrence of VTE was defined as occurrence of DVT or PE symptoms during the period of pregnancy and the first 6 weeks after delivery. Late recurrence of VTE was defined as recurrence of VTE or thrombophlebitis 3 months after delivery.

Secondary outcomes

The secondary outcomes were hemorrhagic pregnancy complications such as mixed hemorrhage, clinically relevant bleeding, early postpartum hemorrhage (within 24 hours post partum), late postpartum hemorrhage (within 6 weeks post partum), and obstetric spinal epidural hematoma. Hemorrhage was defined based on the International Society on Thrombosis and Haemostasis criteria.[18]

Baseline ultrasonography

All pregnant women with a history of DVT were required to be examined by ultrasonography to identify whether there was residual thrombus located in their deep veins. Baseline ultrasonography excluded the effects of previously formed thrombus to the final results.

Statistical analysis

The demographic and obstetrical characteristics and baseline data, including age, ethnicity, body mass index (BMI), and anti-FXa, of participants were collected and analyzed. If χ^2 or Fisher's exact test was used, at least 214 participants were required to provide a significance of 95% (alpha=0.05) and a power of 80% (beta=0.2). Assuming that the number of participants lost to follow-up was close to zero throughout the process, we did not need to adjust the sample size. Two hundred and seventeen participants were recruited to participate in our clinical trial. Categorized variables were expressed as frequency or percentage, and continuous variables were expressed as mean and SD. χ^2 test or Fisher's exact test was used to compare the classification variables. Since group A and group B, group A and group C, and group B and group C were compared separately, the correction of the χ^2 test was recalculated for the level of significance. We used analysis of variance to analyze continuous variables, and an χ^2 test contingency table was constructed to compare the outcomes among the different groups. Statistical analysis was done using SAS V.9.3 software.

RESULTS

Flow chart of the research

As shown in figure 1, we assessed a total of 256 eligible pregnant women in this study. Except for 37 women who were excluded at the beginning of the study, the remaining 219 pregnant women joined the next stage of our trial. They were divided equally into three groups, with 73 participants per group: control group, weight group, and anti-FXa/weight group. Finally, 72 in the control group, 72 in the

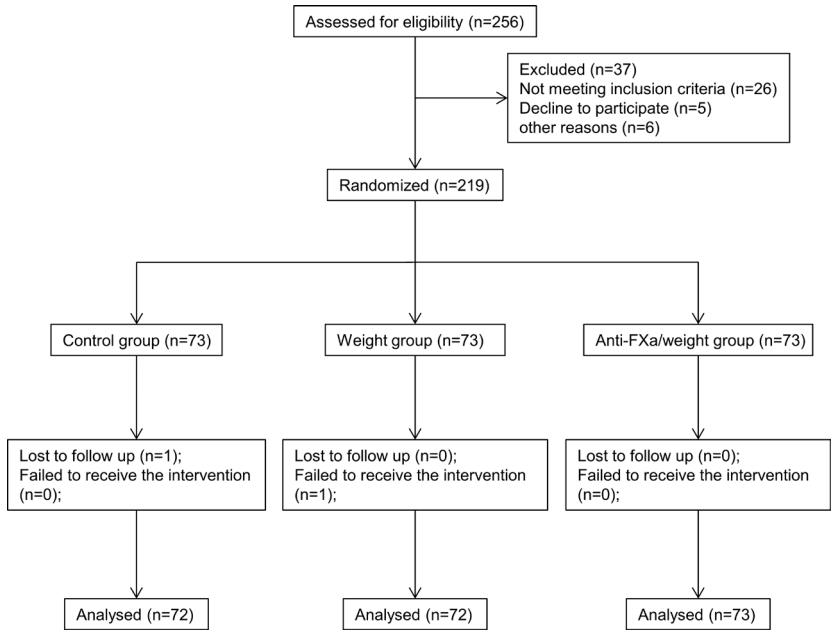

Figure 1 Flow chart of the study. Anti-FXa, anti-factor Xa.

anti-FXa group, and 73 pregnant women in the anti-FXa/weight group received more than 80% of the LMWH treatment using different administration modes and were included in the overall statistics and analysis.

Demographic and obstetrical data of participants

As shown in table 1, there were no significant differences in the demographic and obstetrical characteristics and baseline data, including age, ethnicity, BMI, and anti-FXa level examinations, among the three groups. The number of patients with anti-FXa level <0.2 IU/mL was also similar among these groups: 15 (20.8%) in the control group, 13 (18.1%) in the weight group, and 17 (23.3%) in the anti-FXa/weight group.

Thrombophilia type and prior pregnancy complications among the participants

As shown in table 2, prior placenta-mediated pregnancy complications were not significantly different among the three groups. Factor V mutation and pregnancy loss ranked as the two most common pregnancy complications among the investigated women in the three groups.

Table 1 Demographic and obstetrical data of the participants

	Group A n=72	Group B n=72	Group C n=73	P value
Maternal age, years	30.8±6.5	29.7±6.4	31.1±5.7	0.437
Maternal age >35 years	14 (19.4)	16 (22.2)	17 (23.3)	0.163
Ethnicity				
Han	69 (95.8)	68 (94.4)	71 (97.3)	0.532
Others	3 (4.2)	4 (5.6)	2 (2.7)	0.613
Pregestational body mass index (kg/m^2)	26.5 (4.3)	27.8 (4.7)	27.0 (5.0)	0.559
Cigarette smoker	9 (12.5)	10 (13.9)	7 (9.5)	0.370
Primiparous (first birth)	8 (11.1)	5 (6.9)	7 (9.6)	0.421
Anti-factor Xa level	2.4±0.6	2.3±0.5	2.1±0.8	0.392

Group A: fixed dose group; group B: weight group; group C: anti-FXa+weight group.
FXa, factor Xa.

Obstetric outcomes in the different groups

Compared with group A (55.6%) and group B (61.1%), more women in group C (79.5%) had an expected peak anti-FXa level (0.6–1.0 IU/mL) before delivery. Of the pregnant women in group C, 46 (63.0%) reached the expected peak level of anti-FXa within the treatment range, compared with 34 (47.2%) in group A and 34 (47.2%) in group B, within 1 week after delivery (table 3). There was statistical difference in the percentage of thromboembolism, thrombophlebitis, and postpartum hemorrhage (table 4) after pregnant women were treated with LMWH in different administration modes. Nine (12.5%) women in the control group were diagnosed with thrombophlebitis, while in the weight group and the anti-FXa/weight group four (5.6%) and five (6.8%) women, respectively, suffered from the same complication (p=0.015 and p=0.013). In all patients, heparin administration was either changed or adjusted based on their anti-FXa/weight. After this, we could see that the average anti-FXa level of patients returned to normal. Similarly, five (6.9%) women in the control group developed postpartum hemorrhage, but only one (1.4%) and no woman had the same complication in the other two groups (p=0.014 for group A vs group B; p=0.006 for group A vs group C). In total, there were three patients in group A, one patient in group B, and zero in group C with VTE. There were five patients in group A, one patient in group B, and zero in group C with postpartum hemorrhage. There were seven patients in group A, ten patients in group B, and five patients in group C with pre-eclampsia. A bleeding volume of more than 500 mL within 24 hours after delivery was regarded as postpartum hemorrhage. In this study, all women with postpartum hemorrhage had a bleeding volume of 500–1000 mL within 24 hours after delivery. This result suggested that adjusting the dosage of LMWH according to

Table 2 Thrombophilia type and prior pregnancy complications among the participants

	Group A n=72	Group B n=72	Group C n=73	P value
Type of thrombophilia				
Factor V mutation (homozygote)	9 (12.5)	12 (16.7)	10 (13.7)	0.321
Factor V mutation (heterozygote)	35 (48.6)	44 (61.1)	40 (54.8)	0.455
Prothrombin mutation (homozygote)	4 (5.6)	7 (9.7)	8 (11.0)	0.482
Prothrombin mutation (heterozygote)	8 (11.1)	6 (8.3)	9 (12.3)	0.174
Antithrombin III deficiency	2 (2.8)	1 (1.4)	1 (1.4)	0.464
Protein S deficiency	6 (8.3)	8 (11.1)	7 (9.6)	0.506
Protein C deficiency	1 (1.4)	0 (0)	1 (1.4)	0.543
Antiphospholipid antibody	14 (19.4)	11 (15.3)	13 (17.8)	0.367
High-risk thrombophilia	19 (26.4)	23 (31.9)	25 (34.2)	0.498
Prior pregnancy complications				
Pregnancy losses	35 (48.6)	36 (50.0)	26 (35.6)	0.273
Before 13 weeks	19 (26.4)	14 (19.4)	15 (20.5)	0.412
Between 14 and 22 weeks	12 (16.7)	16 (22.2)	9 (12.3)	0.446
After 23 weeks (intrauterine fetal death)	4 (5.6)	6 (8.3)	2 (2.7)	0.276
Severe pre-eclampsia	8 (11.1)	13 (18.1)	7 (9.6)	0.221
Late severe	8 (11.1)	11 (15.3)	6 (8.2)	0.408
Early severe (<34 weeks)	0 (0)	2 (2.8)	1 (1.4)	0.327
Placental abruption	10 (13.9)	15 (20.8)	13 (17.8)	0.245
Deep vein thrombosis	6 (8.3)	8 (11.1)	8 (11.0)	0.280

Data are expressed as n (%).
High-risk thrombophilia is defined as increase in coagulation factors (I, II, VII, VIII, IX, XII), decrease in protein C activity and protein S, and inhibition of fibrinolytic protein lysis.
Group A: fixed dose group; group B: weight group; group C: anti-FXa+weight group.
FXa, factor Xa.

both weight and anti-FXa could not only prevent VTE but also decrease the incidence rate of postpartum hemorrhage induced by LMWH usage among pregnant women.

Obstetric outcomes of participants in different groups undergoing cesarean section

Similar to the results shown in table 4, the recurrence of both postpartum thromboembolism (p<0.001 for group A vs group C; p=0.015 for group B vs group C) and hemorrhage (p=0.002 for group A vs group C; p=0.015 for group B vs group C) were lower in women during the cesarean section (table 5). The number of patients who suffered from these complications also decreased, and there was statistical difference between the weight group and the weight/anti-FXa group, suggesting that adjusting the dosage of LMWH according to both weight and anti-FXa

Table 3 Anti-FXa peak level among the participants measured antepartum, 1 week post partum and 6 weeks post partum

	Group A n=72	Group B n=72	Group C n=73	A vs B	A vs C	B vs C
Anti-FXa peak level						
Antepartum				0.359	**0.037**	**0.046**
Subtherapeutic (<0.6)	25 (34.7)	20 (27.8)	9 (12.3)			
Therapeutic (0.6–1.0)	40 (55.6)	44 (61.1)	58 (79.5)			
Supratherapeutic (>1.0)	7 (9.7)	8 (11.1)	6 (8.2)			
1 week post partum				0.297	**0.021**	**0.026**
Subtherapeutic (<0.6)	27 (37.5)	29 (40.3)	13 (17.8)			
Therapeutic (0.6–1.0)	34 (47.2)	34 (47.2)	46 (63.0)			
Supratherapeutic (>1.0)	11 (15.3)	9 (12.5)	14 (19.2)			
6 weeks post partum				0.266	**0.018**	0.107
Subtherapeutic (<0.6)	22 (30.6)	16 (22.2)	10 (13.7)			
Therapeutic (0.6–1.0)	42 (58.3)	47 (65.3)	57 (78.1)			
Supratherapeutic (>1.0)	8 (11.1)	9 (12.5)	6 (8.2)			

Data are expressed as n (%).
Data in bold indicates significant difference.
Group A: fixed dose group; group B: weight group; group C: anti-FXa+weight group.
FXa, factor Xa.

Table 4 Obstetric outcomes of the different groups

	Group A n=72	Group B n=72	Group C n=73	A vs B	A vs C	B vs C
Primary outcomes						
Thromboembolism						
Antepartum	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
6 weeks post partum	3 (4.2)	1 (1.4)	0 (0.0)	0.104	**0.012**	0.495
3 months post partum	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
Anti-factor Xa level						
Right after delivery	0.23±0.08	0.25±0.09	0.32±0.12	0.179	**0.019**	**0.027**
6 weeks post partum	0.28±0.11	0.29±0.09	0.45±0.13	0.358	**0.011**	**0.013**
3 months post partum	0.49±0.11	0.47±0.13	0.55±0.15	0.223	0.297	0.314
Thrombophlebitis	9 (12.5)	4 (5.6)	5 (6.8)	**0.015**	**0.013**	0.445
Secondary outcomes						
Spontaneous abortion	0 (0.0)	2 (2.8)	0 (0.0)	0.514	–	0.496
Intrauterine fetal death (>23 weeks)	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
Gestational age at delivery, weeks						
Delivery <37 weeks	7 (9.7)	10 (13.9)	8 (11.0)	0.281	0.466	0.356
Delivery >37 weeks	65 (90.3)	60 (83.3)	65 (89.0)	0.304	0.389	0.355
Placental abruption	4 (5.6)	1 (1.4)	1 (1.4)	0.210	0.307	0.769
Pre-eclampsia	7 (9.7)	10 (13.9)	5 (6.8)	0.580	0.393	0.282
Mild	5 (6.9)	6 (8.3)	3 (4.1)	0.368	0.375	0.276
Late severe	2 (2.8)	4 (5.6)	2 (2.7)	0.464	0.625	0.374
Early severe (<34 weeks)	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
Postpartum hemorrhage	5 (6.9)	1 (1.4)	0 (0.0)	**0.014**	**0.006**	0.495
Within 24 hours	3 (4.2)	1 (1.4)	0 (0.0)	0.176	0.021	0.406
Within 6 weeks	2 (2.8)	0 (0.0)	0 (0.0)	0.532	0.469	–
SEH	1 (1.4)	0 (0.0)	0 (0.0)	0.773	0.635	–
Mode of delivery						
Vaginal	55 (76.5)	51 (70.8)	59 (81.2)	0.611	0.498	0.680
Cesarean	17 (23.6)	19 (26.4)	14 (19.2)	0.473	0.321	0.304
Neonatal birth weight, g	3017.5±459	2976.4±672	3135.4±327	0.320	0.306	0.403
Neonatal birth weight <2500 g	9 (12.5)	11 (15.3)	7 (9.6)	0.495	0.410	0.372
Dalteparin side effects						
Bleeding	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
Thrombotic episodes	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
Skin allergy	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–

Data are expressed as n (%), except for neonatal birth weight which is expressed as mean±SD.
Data in bold indicates significant difference.
Group A: fixed dose group; group B: weight group; group C: anti-FXa+weight group.
FXa, factor Xa; SEH, obstetric spinal epidural hematoma.

level might be more crucial for protecting women during cesarean section.

DISCUSSION

VTE has become a leading cause of maternal and perinatal death[19 20] and has become a global health threat to women and infants.[21 22] In addition, around 30% of cases of VTE are accompanied with PE.[23 24] LMWH with a fixed dosage is commonly recommended as a thromboprophylaxis by the ACCP guidelines: either a prophylactic or intermediate (half therapeutic) dose.[25] It has been reported that treating patients with LMWH in a conservative manner may lead to an increase in other pregnancy complications, such as postpartum hemorrhage and maternal thrombophlebitis.[14 26 27]

LMWH can enhance the activity of anti-FXa and thus promote the enzyme activity of antithrombin III to inhibit coagulation and promote thrombolysis.[28 29] The dosage of heparin to treat VTE in pregnant women must be rather precisely controlled due to its potential risk for hemorrhage.[30]

The distinguished effect of preventing thromboembolism in pregnant women has been reported widely. For instance, in a clinical trial including 284 pregnant women, 6% (95% CI 1.6% to 10.9%) of pregnant women in the control group ended up with VTE without treatment of LMWH during their pregnancy. On the other hand, there was no one in the LMWH-treated group who suffered from pregnancy complications such as VTE, deep VTE, or PE.[31] Another retrospective study recruited 252 pregnant women and

Table 5 Obstetric outcomes of participants in different groups undergoing cesarean section

	Group A n=17	Group B n=19	Group C n=14	A vs B	A vs C	B vs C
Thromboembolism						
6 weeks post partum	2 (11.8)	1 (5.3)	0 (0.0)	0.075	**<0.001**	**0.015**
3 months post partum	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
Thrombophlebitis	6 (35.3)	3 (15.8)	2 (14.3)	0.064	0.032	0.378
Postpartum hemorrhage	4 (23.5)	1 (5.3)	0 (0.0)	0.017	**0.002**	**0.015**
Within 24 hours	3 (17.6)	1 (5.3)	0 (0.0)	0.019	**0.003**	**0.015**
Within 6 weeks	1 (5.9)	0 (0.0)	0 (0.0)	0.124	0.096	–
SEH	1 (5.9)	0 (0.0)	0 (0.0)	0.124	0.096	–
Dalteparin side effects						
Bleeding	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
Thrombotic episodes	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
Skin allergy	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–

Data are expressed as n (%).
Data in bold indicates significant difference.
Group A: fixed dose group; group B: weight group; group C: anti-FXa+weight group.
FXa, factor Xa; SEH, obstetric spinal epidural hematoma.

reached similar conclusions: in the control group, 8 out of 199 pregnant women had severe VTE or PE during pregnancy and postpartum period (4%; 95% CI 2.05 to 7.73); in contrast, of 53 pregnant women, only 1 received additional treatment with LMWH during pregnancy and postpartum period and had VTE (1.9%; 95% CI 0.34 to 10.12).[32] Compared with their findings, our clinical trial also identified that treatment with LMWH during pregnancy could decrease the recurrence of VTE in pregnant women. In addition, we also discovered that a proper dosage of LMWH led to decreased risk of postpartum hemorrhage instead of just promoting thrombolytic effect. Our data indicated that treatment with an appropriate dosage of LMWH could not only inhibit the recurrence of VTE in pregnant women with prior placenta-mediated pregnancy complications, but also facilitate the balance between coagulation and anticoagulation systems during pregnancy.

On the other hand, there are also some researchers who insist that LMWH has little effect on the prevention of VTE in pregnant women. For instance, in a cohort clinical trial involving 270 pregnant women with prior placenta-mediated pregnancy complications, the number of women who suffered from VTE and other pregnancy complications was 0 (95% CI 0% to 1.4%), and there was no statistical relationship between treatment with LMWH and recurrence of VTE.[33] In addition, in a randomized and controlled clinical trial performed in 2016, the authors recruited 144 women at high risk of recurrent VTE and divided them into two groups, treating them with either a fixed dose or adjusting the dose of LMWH according to anti-FXa level. There was no significant difference in morbidity of VTE, DVT, and PE in the two groups, leading to the conclusion that treatment with LMWH could not reduce the recurrence of pregnancy complications.[33] Compared with their research, we recruited more participants in our clinical trial and designed the groups based on a novel criterion.

Previous research has reported that COVID-19 caused a large number of thrombosis cases.[34 35] Accumulating evidence has shown that COVID-19 is an important factor that causes thrombosis in pregnant women,[36] whereas potential treatment that involves inhibitors targeting the virus bears unknown risks especially in pregnant women.[37] Abnormalities in the vascular endothelium, endothelial dysfunction, activation of the renin-angiotensin-aldosterone system, and platelet function abnormalities contribute to thrombogenesis in patients with COVID-19.[38] It has been reported that LMWH is also a crucial agent in the treatment of thromboprophylaxis in pregnant women.[38 39] We hope our research can help clinicians better customize the drug concentration of LMWH for pregnant women with COVID-19. By considering the patient's weight and anti-FXa level together, clinicians can improve LMWH's treatment efficiency in thrombosis and reduce treatment-associated risk in pregnant women with COVID-19.

Due to limited resources and time, only 219 patients were included in this study and the small number of participants might affect the accuracy of the results. A multicenter study could further verify our results and we are trying to extend our research to other hospitals. Second, we mainly identified weight and anti-FXa level as the two crucial factors in determining the dosage of LMWH for pregnant women at high risk of VTE, while many other factors could also be used to more accurately plan the dosage of LMWH, warranting further study on this topic.

CONCLUSION

In conclusion, our research has confirmed that a specific dose of LMWH can be used as a preventive strategy for pregnant women at high risk of VTE. Adjusting the dosage of LMWH according to both the weight and the anti-FXa level of pregnant women could not only prevent VTE but also inhibit postpartum hemorrhage. There were more women in group C whose anti-FXa peak levels were within therapeutic range (0.6–1.0 IU/mL) antepartum, 1 week post partum and 6 weeks post partum. The weight and the anti-FXa level of pregnant women can be used to determine individualized dose of LMWH for VTE treatment.

Contributors SX: literature search, study design, data collection, data analysis and data interpretation. YL and LG: study design, data collection, data analysis, data interpretation and figures. JZ: study design, data collection, data interpretation and figures. LM: study design and data collection. ZY: study design, data analysis and data interpretation, guarantor. All authors contributed to drafting the article or revising it critically for important intellectual content.

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