Published in final edited form as:

Pharmacotherapy. 2011 July ; 31(7): 678–685. doi:10.1592/phco.31.7.678.

Dosing and Monitoring of Low Molecular Weight Heparin in High-Risk Pregnancy: Single Center Experience

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Abstract

Study Objective—To evaluate dosing requirements and monitoring patterns of LMWH when used in high-risk pregnancy.

Design—A retrospective observational cohort study

Setting—University of Illinois at Chicago Medical Center

Patients—Those treated with LMWH from 2001 – 2005 for either prophylaxis or treatment of VTE during pregnancy and monitored with anti-factor Xa activity.

Main Results—Data was obtained on 53 pregnancies in 49 women. Mean starting doses (mg) and doses most proximate to delivery of twice daily enoxaparin were, for prophylaxis and therapeutic groups, respectively, 39.2 (range 30–60) and 55.0 (range 30–100), $p = 0.06$; and 83.0 (range 30–180) and 85.7 (range 30–160), $p = 0.41$. Weight-based mean starting doses (mg/kg) and doses most proximate to delivery were 0.46 vs. 0.62 ($p = 0.03$), and 0.90 vs. 0.87 ($p = 0.29$), for prophylaxis and therapeutic groups, respectively. Dose changes were required in 9/13 (69.2%) and 21/38 (55.2%) patients in the prophylaxis and therapeutic groups, respectively to achieve target anti-Factor Xa activity. The weight-based prophylactic dose was consistently 0.6 mg/kg in all three trimesters achieving a target anti-Factor Xa activity of 0.39 ± 0.18 IU/ml, while the therapeutic dose was 0.9 mg/kg to maintain anti-Factor Xa activity of 0.71 ± 0.22 IU/ml.

Conclusion—Dose changes for LMWH throughout pregnancy as guided by anti-Factor Xa activity were common. A significant increase in the LMWH dose requirements in the prophylactic group suggests that more frequent monitoring of anti-Factor Xa activity may be appropriate in pregnant patients to maintain target anticoagulant levels.

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Presented in part at the 73rd Annual Meeting of the Central Association of Obstetricians and Gynecologists, Las Vegas, NV, October 20, 2006.

Disclosures:

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center For Research Resources.

Keywords

low molecular weight heparin; pregnancy; enoxaparin; anticoagulation; anti-Factor Xa activity; monitoring; dosing

Introduction

Thromboembolism is the leading cause of maternal morbidity and mortality in developed countries.¹ The overall incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) during pregnancy has been estimated at approximately 1 per 1000 pregnancies.² Low molecular weight heparins (LMWH) have a number of advantages over unfractionated heparin including a prolonged plasma half-life which may allow once or twice daily dosing, a more predictable anticoagulant response which may obviate the need for routine laboratory monitoring, and a decreased incidence of heparin induced thrombocytopenia.³

The Eighth American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy provides recommendations for the use of LMWH during pregnancy.³ Additionally, the American College of Obstetrics and Gynecologists issued a Committee Opinion in 2002 stating that LMWH is safe and efficacious in pregnant women and also reported LMWH treatment options for those with an inherited thrombophilia.^{4,5} For acute venous thromboembolism (VTE) treatment, a weight-adjusted therapeutic regimen such as enoxaparin 1 mg/kg every 12 hours is recommended.³ With pregnancy progression, there are increases in maternal weight, increases in renal clearance of LMWH, and increases in the volume of distribution of LMWH, possibly necessitating adjustments in dosing.⁶ To ensure adequate anticoagulation throughout pregnancy, dosing options include 1) adjusting the dose in proportion to the actual weight change or 2) performing anti-Factor Xa activity monitoring (as 4 hour peak levels after steady state has been achieved) and adjusting the LMWH dose to achieve a therapeutic anti-Factor Xa activity of approximately 0.5 to 1.0 IU/mL.^{3,7,8}

For VTE prophylaxis the 2004 ACCP recommendations suggested targeting a prophylactic anti-Factor Xa activity to achieve a peak level of 0.2 – 0.6 IU/mL, but this range is not included as part of the 2008 recommendations, with no specific range currently recommended.^{3,9} Instead, the 2008 ACCP recommendations define a prophylactic dose as enoxaparin 40 mg every 24 hours, dalteparin 5000 units every 24 hours, or tinzaparin 4500 units every 24 hours, with a statement that at extremes of body weight, modifications of the dose may be required. New in the 2008 ACCP recommendations is an intermediate dose LMWH regimen, consisting of enoxaparin 40 mg every 12 hours, or dalteparin 5000 units every 12 hours. The concept of using a target anti-Factor Xa level for VTE prophylaxis remains controversial, with currently acceptable alternatives including the option for the previously defined prophylactic dose, using an intermediate dose LMWH, or periodic monitoring of the anti-Factor Xa activity during pregnancy. The increased renal clearance of LMWH during pregnancy has prompted the latter approach of periodic anti-Factor Xa activity monitoring at our institution. However, the need for this practice remains controversial, since the ideal target range for prophylaxis is unclear at the current time and dose adjustments may not in fact impact safety or efficacy of anticoagulant prophylaxis.

While dosing recommendations for LMWH in pregnancy are fairly well described, monitoring guidelines to attain acceptable anticoagulant safety and efficacy are still needed.^{3,10,11,12,13,14} The primary objective of this study was to evaluate the dosing requirements and monitoring patterns when both therapeutic and prophylactic LMWH is used for anticoagulation during pregnancy.

Materials and Methods

A retrospective observational cohort study of patients given LMWH from 2001–2005 for either prophylaxis or treatment of VTE during pregnancy and monitored with anti-Factor Xa activity was performed. Patients were identified through the University of Illinois at Chicago (UIC) Antithrombosis Center registry and a search of the UIC Maternal Records System (MARS), the electronic obstetrical database. Based on the UIC practice protocol and available literature, our internally targeted goal peak anti-factor Xa levels for all LMWHs were 0.4–0.6 IU/mL for the prophylactic group, 0.6–1.0 IU/mL for the therapeutic group, and 1.0 – 1.5 IU/mL for patients with a mitral valve replacement (MVR).^{9,10,11,12,14} Enoxaparin was dosed as a twice daily regimen, both for prophylactic and therapeutic indications. Initial starting doses included a fixed dose regimen (ie, 30 mg twice daily or 40mg twice daily, depending on provider preference) for prophylaxis and a weight-based dose (typically 1 mg/kg twice daily) for treatment. Routine practice was to try to check peak anti-Factor Xa activity four hours post-dose via a central laboratory once steady-state had been achieved and within a week after dosage initiation or change, and then monthly thereafter once the levels were stable. Since these results were sent to an outside laboratory, there was typically a 2–3 day lag time from the date the sample was collected until the results came back. The frequency of this monitoring was dependent on patient adherence, coordination with other appointments the patients had, and changes in clinical condition. Medication adherence was assessed at every lab draw per patient report and dose changes were only made if adherence was confirmed.

LMWH dose changes were made empirically by the clinician based on these anti-Factor Xa results, considering available syringe strength, insurance limitations, corresponding patient weights, and clinical dosing guidelines.¹⁵ The primary outcome was the change in dosing requirements of LMWH throughout pregnancy as determined by the corresponding anti-factor Xa activity peak levels. Secondary outcomes included the frequency of monitoring as well as thromboembolic events including DVT, PE, cerebral vascular accidents or other vascular occlusions. Major bleeding events were defined as bleeding that led to death, intracranial hemorrhage, retroperitoneal bleeding, or required hospitalization for blood transfusion while minor bleeding was defined as overt bleeding that did not meet the above criteria for major bleeding.

Statistical analysis, performed with SAS c statistical software package (Cary, NC, Version 8.2), included the paired t test (comparison of dosing changes within prophylaxis and therapeutic groups) and descriptive statistics. A $P < 0.05$ was considered statistically significant. The UIC Institutional Review Board approved this study.

Results

Data was obtained on 53 pregnancies in 49 women. Enoxaparin dosed every 12 hours was the LMWH dosing regimen for all patients, with the exception of one with a MVR who received dalteparin every 12 hours. Patient demographics by treatment group are listed in Table 1. Ninety percent of patients were either African American or Hispanic, which reflects the overall demographics of the patients seen at UIC. Table 2 documents the indications for patients receiving either LMWH prophylaxis or therapeutic dosing. For these cases, the term thrombophilia referred to protein C or S deficiency, antithrombin deficiency, antiphospholipid antibody syndrome, Factor V Leiden mutation, or methyltetrahydrofolate reductase mutation.

Dosing parameters for patients taking enoxaparin are presented in Table 3. There was a significant increase from the mean starting doses (mg/kg) compared to doses most

proximate to delivery in the prophylaxis group, 0.46 ± 0.16 vs. 0.62 ± 0.23 ($p=0.03$), but not in the therapeutic group, 0.90 ± 0.17 vs. 0.87 ± 0.19 ($p=0.29$). The mean change in dose (mg/kg) throughout pregnancy was 0.15 ± 0.22 (range -0.2 to $+0.52$) in the prophylaxis group, but only -0.01 ± 0.18 (range -0.45 to $+0.39$) in the therapeutic group. The weight-based dose of LMWH given in each trimester of pregnancy was 0.56 to 0.63 mg/kg for prophylaxis and 0.84 to 0.90 mg/kg for treatment. There was an average of 4.0 ± 2.3 (range 1–8) anti-factor Xa levels obtained per patient in the prophylaxis group and 5.0 ± 2.9 (range 1–17) levels obtained in the therapeutic group. Three or more levels were drawn in 8/13 (61.5%) patients in the prophylaxis group and in 26/38 (68.4%) of the therapeutic group patients. The mean peak anti-factor Xa activity level was 0.39 ± 0.18 IU/mL (range 0.06 – 0.75 IU/mL) in the prophylaxis group and 0.71 ± 0.22 IU/mL (range 0.1 – 1.84 IU/mL) in the therapeutic group.

The case in the therapeutic dosing group with the highest number of anti-Factor Xa levels performed included a patient with a mechanical heart valve, who was checked every 2 weeks due to physician preference, with 17 tests performed during her pregnancy, and 1 dose increase needed. In the prophylactic dosing group, a 58 kg patient that started treatment in the second trimester had her level checked 8 times and required 3 different dose increases, going from a regimen of enoxaparin 30 mg q12h to 60 mg q12h before target anti-Factor Xa levels were achieved.

The time from last dose (hours) until blood draw was 4.1 ± 0.5 and 4.6 ± 2.3 , prophylaxis and therapeutic groups, respectively. The median number of days between levels was 20 (range 13 – 49) and 24 (range 13 – 75), in the prophylactic and therapeutic groups, respectively. In the prophylaxis group, 4/13 (30.8%) patients did not require dosage changes throughout pregnancy, but two patients had only one level drawn, while 9/13 (69.2%) patients did require dosage changes (8 had only increases, 1 had both increases and decreases). Six patients in this group required >1 dose increase. In the therapeutic group, 17/38 (44.7%) patients did not require dosage changes throughout pregnancy, and 21/38 (55.2%) patients did require dosage changes (12 had only increases, 5 had only decreases, and 4 had both increases and decreases). Four patients in this group required > 1 dose increase, and 3 patients required > 1 dose decrease.

Complications (embolic events and hemorrhage) and postpartum anticoagulation regimens are presented in Table 4. One patient who was 42 years old and had a prior PE, chronic hypertension, pregestational diabetes, a body mass index (BMI) of 42kg/m^2 , and no thrombophilias had an uneventful vaginal birth after cesarean at term. A therapeutic dose of LMWH was started 11 hours after delivery and she was discharged home on both 60mg enoxaparin twice daily, (approximately 0.5 mg/kg using her pre-pregnancy weight, no postpartum weight on record) and 7.5mg of warfarin daily. She presented to the emergency room in acute respiratory distress 4 days after delivery and a spiral CT showed bilateral PE and she died in the emergency room. Another patient with antithrombin deficiency and poor adherence to prophylactic doses of enoxaparin 30 mg every 12 hours throughout pregnancy had a PE confirmed by chest CT on postpartum day 10 after a classical cesarean delivery. She subsequently received oral anticoagulation for 6 months. A total of 3 major postpartum hemorrhages requiring transfusions occurred. This included a patient with antithrombin deficiency who was taking prophylactic LMWH and had a failed vaginal birth after cesarean at term. Dense adhesions and uterine extensions complicated the repeat cesarean. She returned to the operating room on the same day as delivery for hypovolemia and hemoperitoneum and the uterine incision was revised. Her last dose of LMWH was 48 hours prior to delivery. Another patient taking prophylactic LMWH, restarted 23 hours post-delivery, had a postpartum hemorrhage after a vacuum assisted delivery with extensive perineal and labial lacerations. The third patient who required a blood transfusion presented

on postpartum day 10 with vaginal bleeding and a supratherapeutic anti-Factor Xa level of 1.36 units/ml. There were 10 minor bleeds, not requiring changes in anticoagulation management. Bruising occurred in 4/13 (30.8%) patients in the prophylactic group, and 22/40 (55%) in the therapeutic (including MVR) group.

Comment

In this retrospective observational cohort study of gravidas maintained on LMWH for prophylaxis or treatment of VTE, LMWH dose changes throughout pregnancy according to anti-factor Xa activity levels were common. A significant increase in the LMWH dose requirements in the prophylactic group suggests that more frequent monitoring of anti-factor Xa levels may be appropriate in pregnant patients if one is to achieve a predetermined target of anti-Factor Xa activity. The weight-based prophylactic dose was consistently 0.6 mg/kg in all three trimesters, achieving the mean target level of 0.39 ± 0.18 IU/ml, in the mid-range of the previously recommended range of 0.2–0.6 IU/ml by ACCP, and on the lower limit of our internally selected range at UIC of 0.4–0.6 IU/ml. The therapeutic weight-based dose was 0.84–0.90 mg/kg, slightly less than the recommended 1.0 mg/kg dose.

Other authors have also commented on the dosage changes in LMWH that result from serial anti-factor Xa levels. For example, Lebaudy et al collected 343 anti-factor Xa levels from 1–49 hours (52% obtained at 3–4 hours) after the last enoxaparin injection in a pharmacokinetic study.¹⁶ The peak anti-Factor Xa levels were lower in pregnant women compared to nonpregnant women and the difference was attributed to increases in enoxaparin clearance. Although the peak anti-Factor Xa levels on a stable dose of 40mg daily of enoxaparin decreased from 0.47 ± 0.13 IU/ml in the first trimester to 0.32 ± 0.08 IU/ml in the third trimester ($P=0.002$), both these mean values were still within the guidelines' recommended range for prophylaxis. The authors also acknowledge that it is not known whether a specific minimum level of anti-Factor Xa activity is necessary to prevent thrombosis. In a review of 321 anti-factor Xa levels in 77 patients receiving VTE prophylaxis with LMWH where 62% received twice daily dosing, only 59% were within the prophylaxis range (defined as 0.2–0.4 IU/ml) despite serial dose adjustments, and 26% were below and 15% were above the range.¹⁷ Furthermore, the number of values within the appropriate range did not change when analyzed with respect to maternal age, gestational age, and BMI. In addition, they found that in patients who were on a prophylactic dose typically reserved for therapeutic dosing, 76.9% of anti-factor Xa levels were still subtherapeutic.

Similar findings have also been reported for therapeutic LMWH dosing. In a study of 37 pregnancies managed with tinzaparin daily at therapeutic doses (0.4–0.7 IU/ml), 45% required one adjustment, 25% required two dose adjustments, and 20% required 3 dose adjustments.¹⁸ Dose adjustments were minor and the median adjustment was 2850 IU. In a study of 15 predominantly obese patients taking 1mg/kg of enoxaparin twice daily, all peak anti-factor Xa levels were therapeutic (defined as 0.5–1.2U/ml), however, 20% of the 8-hour and 73% of the trough levels were sub-therapeutic.¹⁹

Given our findings and those of other investigators, it seems reasonable to serially assess anti-Factor Xa levels in all pregnant women treated with LMWH, because the dose response to LMWH changes throughout pregnancy is not predictable. Although we recognize the limitations, such as lack of laboratory standardization and lack of strong correlation with efficacy and safety outcomes of anti-Factor Xa activity monitoring, to date this is the most practical biological marker that can be used in high risk and special patient populations to indicate the anticoagulant level in the system. Results from our study demonstrated that we achieved higher mean anti-Factor Xa levels (0.39 IU/ml), in the mid-range of the 2004

ACCP recommendations,⁹ but this required a higher overall dose requirement to maintain the prophylactic range, averaging 0.6 mg/kg in every trimester. The current regimen that was put in place in our institution for “prophylaxis” before the 2008 ACCP recommendations now aligns closer with the “intermediate” dose LMWH regimens from ACCP, and is more aggressive than their defined “prophylactic” regimens (dalteparin 5000 units daily, enoxaparin 40 mg daily). Although prior studies have demonstrated no effect from maternal weight on dosing parameters, the greater percentage of obese patients in our population may contribute to these differences.

A prospective trial to evaluate 0.6 mg/kg LMWH dosing every 12 hours for intermediate dosing would now be desirable. A randomized placebo controlled trial comparing enoxaparin 40 mg daily to placebo was of too small of a sample size ($n = 16$) for any conclusive results and demonstrated that poor recruitment may limit the likelihood of these trials in the future.²⁰ Interestingly, the mean LMWH weight-based dose was actually slightly less than that recommended for therapeutic dosing. This too underscores the need for monitoring anti-Factor Xa activity in pregnancy with necessary adjustments. Although limitations of the current study include the small sample size and retrospective nature, this type of data is still needed in order to guide dosing and monitoring of LMWH in pregnancy. We also acknowledge other limitations of our study including the lack of a control group and insufficient power to detect difference in adverse perinatal outcomes.

Both prophylactic and therapeutic LMWH therapy during pregnancy was safe, though LMWH did not prevent all VTE morbidity and mortality. However, our patients often had co-morbidities in addition to VTE risk and these issues may have contributed to some of the adverse outcomes. The two VTE events occurred postpartum, which raises a separate issue of appropriate postpartum anticoagulation. Patients receiving prophylactic doses of LMWH had more bleeding complications with delivery; however, the timing of the LMWH doses and bleeding events suggest these occurrences may not all be related to the anticoagulation. In a case-control study from the same high risk population, there was no increased risk of bleeding complications, including postpartum hemorrhage and the need for transfusion.²¹

The use of LMWH in high-risk pregnancies has become commonplace. Our findings suggest that monitoring and dosing adjustments of LMWH in pregnancy may be necessary for both intermediate-dose and therapeutic dosing regimens. The frequency of anti-Factor Xa monitoring in pregnancy has not been well described, and there are no established recommendations. While limited reports to date show inconsistent results on the necessity of anti-Factor Xa monitoring^{22,23,24} our results suggest that if the desired targets⁹ are to be achieved, anti-Factor Xa monitoring may be desirable. In our practice, we found that monthly anti-factor Xa levels were reasonable to assess the need for dosage adjustments; additional information in the future may obviate the need for such frequent testing. However, despite adequate anti-factor Xa levels and meticulous management of at risk gravidas, VTE events may still occur.

Conclusion

Dose changes for LMWH throughout pregnancy as guided by anti-Factor Xa activity were common. A significant increase in the LMWH dose requirements in the prophylactic group suggests that more frequent monitoring of anti-Factor Xa activity may be appropriate in pregnant patients to maintain target anticoagulant levels.

Acknowledgments

Funding Information: Dr. Nutescu is supported by the University of Illinois at Chicago (UIC) Center for Clinical and Translational Science (CCTS), Award Number KL2RR029878 from the National Center For Research Resources.

The authors would like to acknowledge Soula Angelopoulos, PharmD, for her assistance with IRB submission and data collection.

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Table 1**Demographics**

Parameter	Prophylaxis (n=13 cases)	Therapeutic* (n=40 cases)
Age (mean, years $\pm$ SD)	27.4 $\pm$ 7.5	27.7 $\pm$ 6.1
Race		
African-American (n,%)	7 (53.8%)	26 (65%)
Hispanic (n,%)	5 (38.5%)	10 (25%)
Other (n,%)	1 (7.7%)	4 (10%)
Nulliparity (n,%)	5 (38.5%)	6 (15%)
Initial weight at start of LMWH (mean, kg $\pm$ SD)	85.3 $\pm$ 25.6	89.9 $\pm$ 29.3
Weight gain during pregnancy (mean, kg $\pm$ SD, range)	6.2 $\pm$ 3.7 (1.4–14.1) (n=12)	8.6 $\pm$ 14.1 (–6.0 – 85) (n = 37)
Pre-pregnancy BMI > 30 kg/m ² (n,%)	6 (30.8%)	24 (60%)
Health insurance status		
Public Aid (n,%)	9 (69.2%)	22 (55%)
HMO/PPO (n,%)	3 (23.1%)	19 (45%)
Other (n,%)	1 (7.7%)	0
Trimester LMWH started		
First (n, %)	2 (15.4%)	21 (52.5%)
Second (n, %)	9 (60%)	13 (7.5%)
Third (n, %)	2 (15.4%)	6 (15%)

* Therapeutic group includes patients with MVR

BMI = Body Mass Index

HMO = Health Maintenance Organization

PPO = Preferred Provider Organization

Table 2

Indications for LMWH treatment

Disease	Prophylaxis (n=13 cases)	Therapeutic (n=40 cases)
History of DVT and/or PE	4 (30.8%)	10 (25%)
History of DVT and/or PE and thrombophilia	1 (7.7%)	6 (15%)
Current DVT and/or PE	0	14 (35%)
Current DVT and thrombophilia	0	2 (5%)
Thrombophilia, no VTE	6 (30.8%)	2 (5%)
Mitral valve replacement	0	3 (7.5%)
History of cerebral vein and sinus thrombosis	0	2 (5%)
History of sinus thrombosis and thrombophilia	1 (7.7%)	1 (2.5%)
Maternal disease (Nephrotic syndrome)	1 (7.7%)	0

Table 3

Dosing parameters for patients on enoxaparin given every 12 hours whose weight information was available

Parameter	Prophylaxis n=13	Therapeutic* n=36
Starting LMWH dose (mg) (mean $\pm$ SD, range)	39.2 $\pm$ 9.5 (30 – 60)	83.0 $\pm$ 32.7 (30 – 180)
Ending LMWH dose (mg) (mean $\pm$ SD, range)	55.0 $\pm$ 22.2 (30 – 100)	85.7 $\pm$ 24.7 (30 – 160)
Weight-Based	0.46 $\pm$ 0.16	0.90 $\pm$ 0.17
Starting LMWH dose (mg/kg) (mean $\pm$ SD)		
Weight-Based	0.62 $\pm$ 0.23	0.87 $\pm$ 0.19
Ending LMWH dose (mg/kg) (mean $\pm$ SD)	(n=12) [†]	(n=35) [†]
P value for change in dose mg/kg from start to end	P=0.03	P=0.29
Change in LMWH dose (mg/kg) (mean $\pm$ SD, range)	0.15 $\pm$ 0.22 (–0.2–0.52) (n=12) [†]	–0.01 $\pm$ 0.18 (–0.45–0.39) (n=35) [†]
LMWH dose by Trimester of Pregnancy (mg/kg) (mean $\pm$ SD)		
End of 1 st	0.65 $\pm$ 0.01 (n=2)	0.90 $\pm$ 0.14 (n=18)
End of 2 nd	0.56 $\pm$ 0.15 (n=11)	0.84 $\pm$ 0.15 (n=26)
End of 3 rd	0.63 $\pm$ 0.24 (n=10)	0.86 $\pm$ 0.17 (n=32)

* Excluded dalteparin patient, 1 patient with MVR being treated to higher goal levels, and 2 patients whose weights were not known

[†] Weight data missing on 1 patient in each group

Table 4**Bleeding complications and postpartum anticoagulation**

Parameter	Prophylaxis n=13	Therapeutic n=40
Switched to heparin sodium for delivery (n,%)	(n=12) *5 (38.5%)	(n=36) ‡10 (27.8%)
Time from last injection to delivery (hours, mean ± SD, range)	n = 11 † 48 ± 12 (20–168)	n = 33 † 38 ± 25 (6–144)
Time from delivery until anticoagulation restarted (hours, avg ± SD range)	n = 10 37 ± 42 (12 – 52)	n=35 17 ± 10 (3 – 48)
Postpartum anticoagulation (n, %)	n = 12	n = 39
LMWH alone	0	4 (10%)
LMWH and warfarin	9 (75%)	30 (77%)
LMWH, warfarin, and heparin	1 (8.3%)	2 (5.1%)
None	2 (16.7%)	0
Heparin + warfarin	0	3 (7.7%)
Major Bleeding (n, %)	2 (15.4%)	1 (2.5%)
Minor Bleeding (n, %)	2 (15.4%)	8 (20%)
Bruising (n, %)	4 (30.8%)	22 (55%)
Thromboembolism (n, %)	1 (7.7%)	1 (2.5%)

* n = 12 since one patient transferred her care to another facility at 28 weeks

† n = 11, data missing on remaining 2 patients

‡ n = 36 since 2 patients terminated pregnancy, 1 patient had therapy discontinued before delivery and 1 patient lost to follow up