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Regular Article

The risk of postpartum hemorrhage in women using high dose of low-molecular-weight heparins during pregnancy ☆

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ABSTRACT

Background: Low-molecular-weight heparins (LMWH) are the most commonly used anticoagulant during pregnancy for prevention or treatment of VTE. However, the size of the associated risk of postpartum haemorrhage (PPH) is unknown.
Objective: To assess the bleeding risk of high dose LMWH, also in relation to time between last dose LMWH and delivery.
Material and methods: From 1999 to 2009, we followed 88 pregnant women who were started on therapeutic anticoagulation. Controls were pregnant women without LMWH, matched 1:4 for parity, mode of delivery, age, gestational age and delivery date. PPH was defined as ≥500 ml blood loss for vaginal delivery (severe PPH in vaginal delivery as ≥1000 ml) and ≥1000 ml for cesarean section (CS). Women were divided into subgroups by the interval between last dose of anticoagulation and delivery (<12, 12-24 hrs, >24 hrs).
Results: Risk of PPH after vaginal delivery was 30% and 18% for LMWH-users and non-users, respectively (OR 1.9, 95%CI 1.1-3.5). Risk of severe PPH after vaginal delivery was not different (5.6 vs 5.0%; OR 1.1; 0.4-3.6). Risk of PPH after CS was 12% in LMWH-users and 4% in non-users (OR 2.9; 0.5-19.4). Both events of LMWH-users occurred after emergency CS. The risk of PPH associated with delivery within 24 hours after last dose of LMWH was 1.2 fold higher (95%CI 0.4-3.6) compared to a larger interval.
Conclusion: High dose LMWH carries an increased risk of more than 500 mL blood loss after vaginal delivery. However, this results not in more clinical relevant severe PPHs. The interval between last dose of LMWH and delivery does not influence the risk of PPH.

Introduction

In the general population, 0.5 in 1000 pregnancies [1] is complicated by a venous thrombo-embolism (VTE), with a predominance in the puerperium.[2,3] In women with a previous episode of VTE, the risk of recurrence during pregnancy ranges from 2.4-6.2%.[4,5] For these women, with either a current VTE or a high risk of recurrent VTE, low molecular weight heparin (LMWH) is the most commonly used anticoagulant during pregnancy. The optimal dosage of thromboprophylaxis in women with an increased risk of VTE during pregnancy and puerperium is not established.[6] In our hospital, all pregnant women with an indication for thromboprophylaxis received a high dose intended as a therapeutic dosage of LMWH during pregnancy and the puerperium.

Usage of LMWH during pregnancy may be associated with an increased risk of blood loss or postpartum hemorrhage (PPH), a common complication of childbirth and a leading cause of maternal morbidity and mortality. Few studies assessed the risk of PPH associated with usage of LMWH [7–14], but most studies are retrospective cohort studies, without a control group and describing only a small number of women on therapeutic dosage LMWH.

Further, current guidelines recommend discontinuing LMWH at least 24 hours before labor [6], although no data are available whether this influences the risk of PPH. This is challenging as labor may start unplanned.

We performed a retrospective cohort study in our hospital to evaluate our treatment protocol to assess the bleeding risk with high dose therapeutic dosage LMWH during delivery compared to controls and to assess the bleeding risk in relation to the last injection of LMWH.

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Methods

Patients

This is a retrospective cohort study, including as cases consecutive women who started with a therapeutic dosage LMWH during pregnancy at our hospital between 1999 and 2009. These women were followed prospectively during pregnancy in combined obstetric/ coagulation clinic and seen by a thrombosis specialist every 2 months until 6 weeks post-partum. Indications for anticoagulation were a history of idiopathic, provoked or pregnancy related VTE, recurrent fetal loss or asymptomatic thrombophilic defects (protein C, S or AT deficiency). For a given woman, we included only the first ongoing pregnancy in which she used anticoagulation, to avoid selection bias. Pregnancies with early fetal loss were not included. Detailed information on episodes of VTE, external risk factors for thrombosis, obstetric history, anticoagulant treatment and delivery was collected using a standardised questionnaire. Data on labor was collected retrospectively by reviewing medical records. National legislation and the ethical committee of our institution approve this type of studies without the need for review of the protocol.

Treatment Protocol

Women were started on a therapeutic dosage of nadroparin once daily in early pregnancy with bodyweight adjusted therapeutic dosage (175 anti-Xa IU kg^{-1} day^{-1}), as soon as a pregnancy test was positive or when a VTE occurred during pregnancy. All women were followed by a thrombosis specialist every 2 months until 6 weeks post-partum. Anti-fXa levels were not routinely monitored and doses of LMWH were not adjusted for increasing bodyweight or increasing renal clearance. If hypersensitivity skin reactions developed, we switched to another preparation, fondaparinux, danaparoid or acenocoumerol. The women had no planned induction of labor with withholding of anticoagulation, but all women switched to divided (twice daily) dosing of their LMWH in the 37th week to minimize the bleeding risk. Women who used acenocoumerol switched to a twice daily dosing LMWH in the 37th week. Second, LMWH or another preparation was stopped at the start of spontaneous or induced labor and restarted 4–8 hours after delivery (when blood loss was normal) and stopped six weeks postpartum. Women with a current VTE during pregnancy were treated for six months, but at least until six weeks postpartum.

Controls

Controls were women who delivered in our hospital and did not use LMWH or another anticoagulant during pregnancy. LMWH users were matched 1:4 to controls (non-users) by random electronic selection for parity, mode of delivery, age, gestational age, and date of delivery (+/− 2 years). Exclusion criteria for the controls were a history of VTE or PPH.

Definitions

The amount of blood loss was a visual estimation. According to the WHO guidelines, we defined ≥500 ml as definition of PPH for vaginal delivery and ≥1000 ml for a cesarean section. Severe PPH was defined as ≥1000 ml for a vaginal delivery. Primary and secondary PPH were defined as a bleeding within 24 hours after delivery and after 24 hours, respectively [15].

Statistical Analysis

Continuous variables were expressed as mean or median values and standard deviations or ranges depending on normality, categorical data as counts and percentages. Differences between groups were evaluated by the student *t* test or Mann–Whitney *U* test, depending on the normality of data for continuous data, and by Fisher exact test for categorical data. A two-tailed p-value of less than 0.05 was considered statistically significant. Women were divided into subgroups by the various intervals between last dose of LMWH and delivery (<12 hrs, 12–24 hrs, >24 hrs). Logistic regression was performed for calculating odds ratios for PPH in users and non-users and in relation to timing of last injection of LMWH with adjustment for known risk factors for PPH, such as age, parity and birth weight >4000 gram. Statistical analyses were performed using PASW version 18.0 (IBM SPSS, Chicago, Illinois, United States).

Results

We followed 143 pregnancies in 88 women. We included 88 first pregnancies in which women used full dose anticoagulation. Baseline characteristics are shown in Table 1. Median age was 30 yrs (range 20–43 yrs), 66% was nulliparous. All women started with nadroparin. Sixty-eight percent (n = 60) used LMWH during the whole pregnancy, 17 (19%) women switched to acenocoumarol between 16 and 36 weeks, 9 (10%) switched to fondaparinux, 2 (2%) switched to danaparoid and one woman switched to unfractionated heparin during labor. The reason for switching was mostly hypersensitivity skin reactions or (for VKA) the wish to avoid injections. All women used a dosage of anticoagulation intended as therapeutic during pregnancy.

Modes of deliveries were vaginal in 81% and cesarean section (CS) in 19% (9% elective, 10% emergency). Labor was induced in 26 of 88 women: this was in 17/71 (24%) women who had a vaginal delivery, 1/9 (11%) of the women who had an emergency CS and 8 women who had a primary CS. Median gestational age was 39 0/7 weeks (28 3/7-42 3/7). One late fetal loss in the 30th week due to abruptio placenta was reported in this cohort. In total, 3 pregnancies were complicated by preeclampsia and 3 by HELLP syndrome.

Bleeding Complications During Pregnancy

Of the 88 patients, 5 (6%) had vaginal blood loss during pregnancy without gynecological abnormalities. All these women used LMWH. One patient had epistaxis around the 20th week and 10% had hematoma due to injection of the LMWH. No other bleeding episodes were reported.

Bleeding Complications During and After Delivery

Risk of PPH after vaginal delivery was 30% vs. 18% for LMWH-users and non-users, respectively (OR 1.9; 95%CI 1.1-3.5; p = 0.029). Risk of

Table 1
Baseline characteristics.

	LMWH users (n = 88)	Non-users (n = 352)
Median age at pregnancy, years	30	30
Median gestational age at delivery, weeks	39 0/7	39 4/7
Median birthweight, gram	3360	3360
Aspirin use	0	0
Indication for anticoagulation, n(%)		
History of VTE	64 (73)	
Recurrent fetal loss	5 (6)	
Asymptomatic thrombophilic defects‡	14 (16)	
VTE in current pregnancy	5 (6)	
Mode of delivery, n		
Vaginal, normal delivery	65	260
Vaginal, assisted	6	24
Cesarean section, primary	8	32
Cesarean section, secondary	9	36

‡ Antithrombin, protein C and protein S deficiency.

severe PPH (≥1000 ml) after vaginal delivery was comparable between both groups (5.6 vs 5.0%; OR 1.1; 95%CI 0.4-3.6; p = 0.83). Of the LMWH-users who had a severe PPH after vaginal delivery (4/71), 2 had uterine atony, one had retained placenta and one had a PPH after vacuum extraction due to uterine atony. Risk of PPH in women who delivered by CS was 12% (2/17) in LMWH-users and 4% (3/67) in non-users (OR 2.9; 95%CI 0.5-19.4; p = 0.26). Both events in LMWH-users occurred after emergency CS, but both had their last injection of LMWH > 12 hours before the CS. See also Table 2. The reasons for emergency CS were fetal distress (n = 5), prolonged 2nd stage of labor (n = 1) and a prolonged 1st labor. (n = 3). None of the women with a pregnancy complicated by HELLP-syndrome or pre-eclampsia experienced a severe PPH.

Of the women who used danaparoid (n = 2) and unfractionated heparin (n = 1) during delivery, none experienced a PPH. Of the women who used fondaparinux during delivery (n = 9), one experienced a PPH, but she had her last injection 48 hours before.

The amount of blood loss after vaginal delivery is presented in Fig. 1, showing an increased percentage of women with PPH (blood loss 500 ml or more), but not of severe PPH (over 1000 ml). Of note, the median blood loss was comparable after primary (350 vs 325 ml; p = 0.79) and emergency CS (425 vs 400 ml; p = 0.29) in users vs non-users, respectively.

In total, 8% (2/26) of LMWH users vs 11% (8/73) of the non-users who experienced a PPH, needed red blood cell (RBC) transfusion (p = 0.46).

Finally, one woman who used LMWH experienced a secondary PPH (>24 hrs).

Timing of Last Injection LMWH and Risk of Bleeding

Of the 88 women with anticoagulation during first pregnancy (LMWH users), 10 women delivered within 12 hours after the last injection of LMWH, 37 women within 12–24 hours and 26 women after 24 hours. In 15 women (17%), the timing was unknown. The time between last injection and delivery of the women who delivered within 12 hours ranged from 5 to 11 hours, with a median of 6 hours. Median blood loss in women who delivered before 12 hours after last dose of LMWH was comparable to 12–24 hours and after 24 hours (275 vs 350 vs 325 ml; p = 0.30). Risk of a PPH after vaginal and CS delivery was 30%, 38% and 27% for intervals of <12, 12–24 and >24 hours, respectively (p = 0.36). Risk of a severe PPH was 0%, 11% and 4% for intervals of <12, 12–24 and >24 hours, respectively (p = 0.58). Overall, the risk of PPH within 24 hours after the last injection of LMWH did not significantly differ from the risk in women who delivered more than 24 hours after the last injection (OR 1.4; 95% CI 0.5-3.9; p = 0.56). After adjustment for age, birthweight >4000 gram and parity, OR was 1.2 (95% CI 0.4-3.6; p = 0.73). See for detailed data Table 3. In 17% of the women (n = 15) we had missing data about the timing of last injection of LMWH, but their median blood loss was comparable with the women who delivered within and after 24 hours (300 vs 350 vs 249 ml; p = 0.21).

Of the women who had a planned induction of labor, 50% delivered within 24 hours after the last dose of LMWH and of the women who had spontaneous onset of labor 58% delivered within 24 hours. After adjustment for parity, age and birthweight >4000 gram, LMWH-users who had a spontaneous onset of labor had a 1.9 fold increased risk for PPH compared to women who had a planned induction of labor (95% CI 0.6-5.8; p = 0.29).

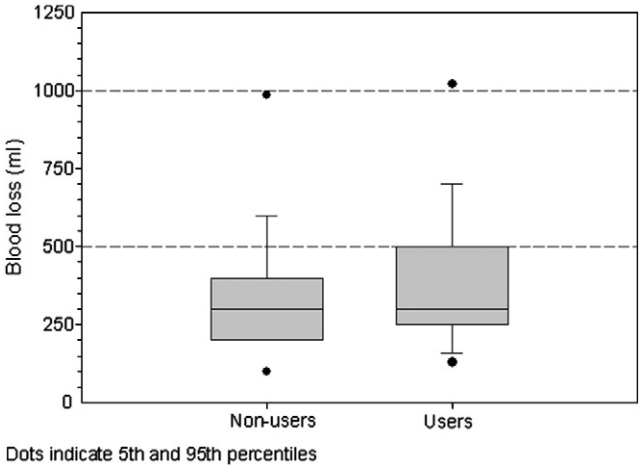

Fig. 1. Blood loss after vaginal delivery in users vs non-users.

Thrombo-embolic Complications

No recurrent VTE was reported in the women who used therapeutic dosage LMWH because of a history of VTE. Five women had a current VTE during the pregnancy, one woman had a recurrent VTE in the 8th week and one woman in the 34th week of pregnancy while they had not yet started their thromboprophylaxis. Three patients had a first VTE in 8th, 10th and 37th week of pregnancy and started with therapeutic dosage of LMWH.

Table 2
Risk of PPH in relation to mode of delivery.

%	LMWH users (n = 88)	Non-users (n = 352)	p-value	OR (95%CI)
Overall				
500 ml	29.5	23.6	0.08	1.6 (0.9-2.7)
1000 ml	6.8	4.8	0.46	1.4 (0.5-3.8)
Vaginal delivery (overall)				
500 ml	29.6	17.8	0.029	1.9 (1.1-3.5)
1000 ml	5.6	5.0	0.83	1.1 (0.4-3.6)
Vaginal delivery (spontaneous)				
500 ml	26.1	15.8	0.058	1.9 (1.0-3.6)
1000 ml	4.6	3.8	0.79	1.2 (0.3-4.5)
Vaginal delivery (assisted)				
500 ml	66.7	37.5	0.21	3.3 (0.5-22.0)
1000 ml	16.7	16.6	1.0	1.0 (0.1-11.1)
Cesarean section (overall)				
1000 ml	11.7	4.4	0.26	2.9 (0.5-19.4)
Cesarean section (primary)				
1000 ml	0	6.3	0.45	
Cesarean section (emergency)				
1000 ml	22.2	2.8	0.06	11.3 (1.0-145.5)

Table 3
Risk of PPH based on interval between last injection of LMWH and delivery.

	<24 hrs	>24 hrs	OR (95%CI)	OR (95%CI)‡	p ‡
Overall					
MBL, ml	300	350			
PPH, %	34.7	28.0	1.4 (0.5-3.9)	1.2 (0.4-3.6)	0.73
Vaginal delivery					
MBL, ml	300	300			
PPH (≥500 ml), %	35.0	26.3	1.5 (0.5-5.1)	1.3 (0.4-4.8)	0.68
Cesarean section					
MBL, ml	400	400			
PPH (≥1000 ml), %	11.1	16.7	0.7 (0.03-12.4)	0.4 (0.1-21.4)	0.67

‡ adjusted for age, parity and birthweight >4000 gram; MBL: median blood loss.

Comments

In this study, we analysed the bleeding risk of high dose LMWH during pregnancy and the puerperium in 88 pregnancies. We showed that women who used LMWH had a 1.9-fold increased risk for PPH, but this did not result in more RBC transfusions. We observed no increased risk for a severe PPH after vaginal delivery. The PPH risk was not increased in women who delivered within 24 hours after the last injection of LMWH as compared to women who delivered more than 24 hours after the last dose LMWH.

Overall, we reported 30% PPH (≥500 mL) and 6% severe PPH after vaginal deliveries in women who used LMWH. There are a few studies who also reported the bleeding risk of high dose or therapeutic dosage of LMWH.[7,10,13,16] Kominiarek et al. [7] reported no increased bleeding risk in a case–control study of 49 women using LMWH during pregnancy. Sixty-seven percent used a therapeutic dosage of LMWH, but they did not analyse the risk of therapeutic dosages separately. Furthermore 70% had more than 24 hours between last dose of LMWH and delivery. Voke et al.[13] reported a 5% incidence of primary PPH (≥500 mL) in 126 women with a VTE during the current pregnancy followed by therapeutic dosage LMWH, but there was no control-group. Rowan et al.[10] described no bleeding complications in 32 pregnancies with therapeutic dosage of LMWH, but 26 of these women had a planned induction of labor. Lepercq et al.[16] described 624 pregnancies of which 49 women used a therapeutic dosage of enoxaparin. They found no increased bleeding risk, but did not analyse the pregnancies with therapeutic dosage separately.

We observed 18% PPH and 5% severe PPH in our matched controls after vaginal delivery. This is comparable with findings of a population-based cohort analysed in the Netherlands, which showed a risk for PPH (≥500 ml) and severe PPH (≥1000 ml) of 19% and 4.2% after vaginal delivery, respectively.[15] There is no single, satisfactory definition for PPH worldwide. In the Netherlands a PPH is defined as ≥1000 ml blood loss for a vaginal delivery and a cesarean section. Because different countries and the WHO define PPH as more than 500 ml blood loss after vaginal delivery, we also used these cut-off values for the analysis. We observed no increased risk for a severe PPH after a vaginal delivery. Moreover, Fig. 1 shows that the distribution of the amount of blood loss lies mainly below 1000 mL. This amount of blood loss is usually not clinical relevant, because this leads mostly not to a RBC transfusion and an extension of the hospital stay.

In our cohort women started with a therapeutic weight-adjusted once daily dosage of LMWH in the beginning of their pregnancy until 37 weeks of gestation. During pregnancy LMWH requirements may alter because the glomerular filtration rate increases in the 2nd trimester and the volume of distribution of LMWH changes. Given these physiologic changes, Crowther et al.[17] suggested that the dosage of LMWH should be increased in proportion to the change in body-weight. However, adjustment of the dose of LMWH according to anti-fXa levels and increasing body-weight is controversial. Some small studies showed that periodic (every 1–3 months) dose-adjustment to maintain therapeutic anti-fXa levels is essential.[18,19] However, other studies demonstrated that only a few women require dose adjustment when therapeutic doses of LMWH are used.[20–22] Therefore, in the absence of large studies with clinical end-points of optimal dosage during pregnancy we decided to not routinely monitor anti-fXa levels and not to adjust the doses for increasing body-weight or increasing renal clearance.

The women who received their last injection of LMWH within 24 hours before delivery had no increased bleeding risk compared to women who delivered after 24 hours. The ACCP guidelines recommend a weight-adjust twice-daily dosage LMWH and discontinuation of LMWH at least 24 hours prior to elective induction of labor (Grade 1 C).[6] In our hospital women who use anticoagulation for (prevention of) VTE have no standard planned induction of labor, but all women switched to divided therapeutic weight-adjusted dosing of LMWH in the 37th week to minimize the bleeding risk. However, dividing the LMWH dose into twice daily doses and stopping at start of labor may decrease the anticoagulant effect at delivery. In total, only 30% of the women in our cohort had a planned labor. The incidence of PPH in the women who had a spontaneous labor seems to be higher compared to women with a planned labor, (OR 1.9; 95% CI 0.6-5.8; p = 0.29) but not reaching statistical significance. This difference cannot be explained by a longer duration between delivery and the last dose of LMWH, because the number of women who delivered within 24 hours was comparable in both groups. Reassuringly, in women who delivered within 12 hours after last dose of LMWH, no severe PPH occurred and no woman needed a RBC transfusion. One study by Maslovitz et al.[8] described the bleeding risk postpartum related to the timing of last injection of LMWH. They found no increased bleeding risk in the women who delivered within 24 hours, but most of these patients (84%) had only a prophylactic dosage of enoxaparin.

Our study has some limitations. Firstly, the amount of blood loss was not objectively measured, but as in common clinical practice the blood loss was a visual estimation. It is known that this gives mostly an underestimation of the amount of blood loss[23–25], in particular a higher estimated blood loss (>500 ml) is associated with a greater underestimation.[26] In our cohort we observed an increased risk for a ≥500 ml blood loss in vaginal delivery but no increased risk for ≥1000 ml. The latter could be explained by visual underestimation of especially the higher amounts of blood loss.

Secondly, the obstetricians attending the birth were not blinded and may have managed the third stage of labour differently in an anticoagulated patient either by administering prophylactic agents (i.e. oxytocics) or intervening earlier to prevent PPH. However, all women (users and non-users) who deliver in our hospital have an active management of the third stage of labor, including oxytocin. Thirdly, we did not evaluate the therapeutic anticoagulant effect with objective laboratory analyses. Therefore, it may be possible that a proportion of patients did not reach therapeutic levels of LMWH in the third trimester. Finally, the collecting of data about the delivery and timing of last dose of LMWH retrospectively is a limitation. Consequently, we had 17% missing data about the timing and two women with missing data had a PPH. However, the median blood loss of these women was comparable with the women without missing data.

Given the increased risk of PPH for vaginal and emergency CS delivery in women using full dose LMWH for prevention of VTE during pregnancy, the individual risk of VTE and PPH should be balanced. We will reconsider our treatment protocol, maybe in a subgroup of patients a prophylactic dose of anticoagulation during pregnancy might result in more net benefit.[27] A randomized trial comparing full dose LMWH with prophylactic dose LMWH in pregnant women with an increased risk of VTE is needed to improve patient care.

In conclusion, high dose LMWH carries an increased risk of PPH after vaginal delivery. However, it does not lead to an increased risk for a severe and clinical relevant PPH. It is unknown whether this risk is offset by a lower risk of (recurrent) VTE. Secondly, PPH risk seems to not be increased after deliveries within 24 hours after the last injection of LMWH compared to women who delivered after 24 hours.

Conflict of Interest Statement

None of the authors declare a conflict of interest.

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H.M. Knol and K. Meijer conceived the study idea, L. Schultinge and H.M. Knol collected the data, all authors contributed to the

study design, data abstraction and interpretation. H.M. Knol wrote the manuscript and all authors took part in its revision and approved the final version.

References

[1] Toglia MR, Weg JG. Venous thromboembolism during pregnancy. N Engl J Med 1996;335:108–14.
[2] Jacobsen AF, Skjeldestad FE, Sandset PM. Incidence and risk patterns of venous thromboembolism in pregnancy and puerperium–a register-based case–control study. Am J Obstet Gynecol 2008;198:233–7.
[3] Ray JG, Chan WS. Deep vein thrombosis during pregnancy and the puerperium: a meta-analysis of the period of risk and the leg of presentation. Obstet Gynecol Surv 1999;54:265–71.
[4] Pabinger I, Grafenhofer H, Kaider A, Kyrle PA, Quehenberger P, Mannhalter C, et al. Risk of pregnancy-associated recurrent venous thromboembolism in women with a history of venous thrombosis. J Thromb Haemost 2005;3:949–54.
[5] Brill-Edwards P, Ginsberg JS, Gent M, Hirsh J, Burrows R, Kearon C, et al. Safety of withholding heparin in pregnant women with a history of venous thromboembolism. Recurrence of Clot in This Pregnancy Study Group. N Engl J Med 2000;343:1439–44.
[6] Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:844S–86S.
[7] Kominiarek MA, Angelopoulos SM, Shapiro NL, Studee L, Nutescu EA, Hibbard JU. Low-molecular-weight heparin in pregnancy: peripartum bleeding complications. J Perinatol 2007;27:329–34.
[8] Maslovitz S, Many A, Landsberg JA, Varon D, Lessing JB, Kupferminc MJ. The safety of low molecular weight heparin therapy during labor. J Matern Fetal Neonatal Med 2005;17:39–43.
[9] Dulitzki M, Pauzner R, Langevitz P, Pras M, Many A, Schiff E. Low-molecular--weight heparin during pregnancy and delivery: preliminary experience with 41 pregnancies. Obstet Gynecol 1996;87:380–3.
[10] Rowan JA, McLintock C, Taylor RS, North RA. Prophylactic and therapeutic enoxaparin during pregnancy: indications, outcomes and monitoring. Aust N Z J Obstet Gynaecol 2003;43:123–8.
[11] Nelson-Piercy C, Letsky EA, de Swiet M. Low-molecular-weight heparin for obstetric thromboprophylaxis: experience of sixty-nine pregnancies in sixty-one women at high risk. Am J Obstet Gynecol 1997;176:1062–8.
[12] Sanson BJ, Lensing AW, Prins MH, Ginsberg JS, Barkagan ZS, Lavenne-Pardonge E, et al. Safety of low-molecular-weight heparin in pregnancy: a systematic review. Thromb Haemost 1999;81:668–72.
[13] Voke J, Keidan J, Pavord S, Spencer NH, Hunt BJ. The management of antenatal venous thromboembolism in the UK and Ireland: a prospective multicentre observational survey. Br J Haematol 2007;139:545–58.
[14] Bauersachs RM, Dudenhausen J, Faridi A, Fischer T, Fung S, Geisen U, et al. Risk stratification and heparin prophylaxis to prevent venous thromboembolism in pregnant women. Thromb Haemost 2007;98:1237–45.
[15] Bais JM, Eskes M, Pel M, Bonsel GJ, Bleker OP. Postpartum haemorrhage in nulliparous women: incidence and risk factors in low and high risk women. A Dutch population-based cohort study on standard (> or =500 ml) and severe (> or =1000 ml) postpartum haemorrhage. Eur J Obstet Gynecol Reprod Biol 2004;115:166–72.
[16] Lepercq J, Conard J, Borel-Derlon A, Darmon JY, Boudignat O, Francoual C, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. BJOG 2001;108:1134–40.
[17] Crowther MA, Spitzer K, Julian J, Ginsberg J, Johnston M, Crowther R, et al. Pharmacokinetic profile of a low-molecular weight heparin (reviparin) in pregnant patients. A prospective cohort study. Thromb Res 2000;98:133–8.
[18] Barbour LA, Oja JL, Schultz LK. A prospective trial that demonstrates that dalteparin requirements increase in pregnancy to maintain therapeutic levels of anticoagulation. Am J Obstet Gynecol 2004;191:1024–9.
[19] Jacobsen AF, Qvigstad E, Sandset PM. Low molecular weight heparin (dalteparin) for the treatment of venous thromboembolism in pregnancy. BJOG 2003;110:139–44.
[20] Rodie VA, Thomson AJ, Stewart FM, Quinn AJ, Walker ID, Greer IA. Low molecular weight heparin for the treatment of venous thromboembolism in pregnancy: a case series. BJOG 2002;109:1020–4.
[21] Rey E, Rivard GE. Prophylaxis and treatment of thromboembolic diseases during pregnancy with dalteparin. Int J Gynaecol Obstet 2000;71:19–24.
[22] Smith MP, Norris LA, Steer PJ, Savidge GF, Bonnar J. Tinzaparin sodium for thrombosis treatment and prevention during pregnancy. Am J Obstet Gynecol 2004;190:495–501.
[23] Patel A, Goudar SS, Geller SE, Kodkany BS, Edlavitch SA, Wagh K, et al. Drape estimation vs. visual assessment for estimating postpartum hemorrhage. Int J Gynaecol Obstet 2006;93:220–4.
[24] Gharoro EP, Enabudoso EJ. Relationship between visually estimated blood loss at delivery and postpartum change in haematocrit. J Obstet Gynaecol 2009;29:517–20.
[25] Stafford I, Dildy GA, Clark SL, Belfort MA. Visually estimated and calculated blood loss in vaginal and cesarean delivery. Am J Obstet Gynecol 2008;199:519.e1-7.
[26] Razvi K, Chua S, Arulkumaran S, Ratnam SS. A comparison between visual estimation and laboratory determination of blood loss during the third stage of labour. Aust N Z J Obstet Gynaecol 1996;36:152–4.
[27] Roeters van Lennep JE, Meijer E, Klumper FJ, Middeldorp JM, Bloemenkamp KW, Middeldorp S. Prophylaxis with low-dose low-molecular-weight-heparin during pregnancy and postpartum: is it effective? J Thromb Haemost 2011;9:473–80.