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Incidence of postpartum haemorrhage in women receiving therapeutic doses of low-molecular-weight heparin: results of a retrospective cohort study

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ABSTRACT

Background: Low-molecular-weight heparin (LMWH) is the drug of choice to prevent venous thrombosis in pregnancy, but the optimal dose for prevention while avoiding bleeding is unclear. This study investigated whether therapeutic doses of LMWH increase the incidence of postpartum haemorrhage (PPH) in a retrospective controlled cohort.

Methods: All pregnant women who received therapeutic doses of LMWH between 1995 and 2008 were identified in the Academic Medical Center, Amsterdam, The Netherlands. The controls were women registered for antenatal care in the same hospital who did not use LMWH during pregnancy, matched by random electronic selection for age, parity and delivery date to LMWH users. The incidence of PPH (blood loss >500 ml), severe PPH (blood loss >1000 ml) and median blood loss were compared in two cohorts of LMWH users and non-users.

Results: The incidence of PPH was 18% in LMWH users (N=95) and 22% in non-users (N=524) (RR 0.8; 95% CI 0.5 to 1.4). The incidence of severe PPH was 6% in both groups (RR 1.2; 0.5 to 2.9). The median amount of blood loss differed only in normal vaginal deliveries. It was 200 ml in LMWH users and 300 ml in non-users (difference −100 ml; 95% CI −156 to −44).

Conclusion: Therapeutic doses of LMWH in pregnancy were observed not to be associated with a clinically meaningful increase in the incidence of PPH or severe PPH in women delivered in this hospital, although this observation may be confounded by the differential use of strategies to prevent bleeding. A randomised controlled trial is necessary to provide a definite answer about the optimal dose of LMWH in pregnancy.

ARTICLE SUMMARY

Article focus

- To compare the incidence of PPH (ie, blood loss >500 ml in the first 24 h of delivery) in two cohorts of pregnant women who were treated with therapeutic doses of LMWH and those who were not.
- To compare the incidence of severe PPH (blood loss >1000 ml) in two cohorts of pregnant women who were treated with therapeutic doses of LMWH and those who were not.
- To compare the median blood loss in two cohorts of pregnant women who were treated with therapeutic doses of LMWH and those who were not.

Key message

- Therapeutic doses of LMWH in pregnancy were not associated with a clinically meaningful increase in the incidence of PPH (RR 0.8; 95% CI 0.5 to 1.4) or severe PPH (RR 1.2; 0.5 to 2.9) in women delivered in our hospital.
- The median amount of blood loss differed only in normal vaginal deliveries. It was lower in LMWH users (200 ml) than in non-users (300 ml) (difference −100 ml; 95% CI −156 to −44).

Strength and limitation of this study

- This is the largest cohort of pregnancies treated with high doses of LMWH.
- Although this was a controlled cohort study, it is likely that strategies to decrease the risk of PPH differed between women who were treated with LMWH and controls.

Low-molecular-weight heparin (LMWH) is the drug of choice in pregnant women requiring prophylaxis or treatment for venous thrombosis. However, the optimal dose with respect to efficacy and safety is uncertain.[1] LMWH has the disadvantage that its anticoagulant effect can only be partly antagonised. This is of particular importance with respect to its use in high doses and raises concerns about an increased risk of bleeding, most notably postpartum haemorrhage (PPH), when used in pregnant women.

PPH is defined by the WHO as postpartum blood loss in excess of 500 ml.[2] However, as other definitions have been suggested,[3] we

classified blood loss more than 1000 ml as severe PPH. PPH has an incidence of 19% in nulliparous deliveries in The Netherlands.[4] The diagnosis encompasses excessive blood loss from the uterus, cervix, vagina and perineum. The commonest cause of primary PPH (PPH <24 h following delivery) is uterine atony.[5] In order to limit the risk of PPH, current guidelines recommend the discontinuation of LMWH 12–24 h before delivery.[1 6] However, as labour can commence spontaneously, timely discontinuation cannot be guaranteed. The risk of PPH associated with the use of LMWH has been assessed in several studies.[3 7–13] These studies either included a small or an unknown number of women treated with therapeutic doses of LMWH[3 7–10] or they lacked a control group of women who did not use LMWH.[7 9–11 13] Only two studies report the bleeding risk associated with antepartum therapeutic doses of LMWH: a prospective multicentre survey in the UK and Ireland and a systematic review of studies about LMWH use in pregnancy.[11 13] Blood loss more than 500 ml was observed in six of 126 (4.8%) and three of 174 (1.7%) women who were treated with therapeutic doses of LMWH in the two studies, respectively. On the other hand, significant failure rates have been observed despite prophylaxis with low-dose LMWH in pregnancy.[14–16] In our hospital, pregnant women who we judge to require anticoagulant prophylaxis are treated with therapeutic doses of LMWH. This protocol was based on a systematic review that we performed in 1998.[14] In this review of several cohorts of women, recurrent venous thromboembolism (VTE) occurred in 2.0% (3/149) of pregnant women, all of whom were treated with prophylactic or intermediate doses of LMWH. Similar findings were reported in another large cohort study in which seven out of eight recurrent episodes of VTE occurred in women on prophylactic or intermediate doses of enoxaparin.[15]

We performed a controlled cohort study in our hospital to assess the risk of PPH associated with therapeutic doses of LMWH in pregnant women.

MATERIALS AND METHODS

Identification of study cohorts

By hospital protocol, anti-Xa levels were measured at 1-month intervals in women who were treated with therapeutic doses of LMWH or heparinoid during pregnancy. Our study cohort was thus identified by the collection of hospital ID numbers in whom anti-Xa measurements were performed between mid-August 1995 and mid-February 2008. We reviewed charts to assess whether the anti-Xa measurements were performed during pregnancy. Inclusion criteria were: therapeutic doses of LMWH, pregnancy duration of at least 25 weeks' gestation and delivery in the Academic Medical Center (AMC).

The control cohort consisted of women who had been registered for antenatal care in the AMC before 24 weeks' gestational age, delivered in the AMC and did not use LMWH during their pregnancy. Women treated with LMWH and controls were matched by random electronic selection for age (±2 years), parity (nulliparous or multiparous) and date of delivery (±1 year) in a 1:6 ratio. This study was approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam.

Intervention

The hospital protocol was to base LMWH doses on body weight before pregnancy, in which the therapeutic dose of LMWH was prescribed according to the manufacturer (table 1).

All women were seen at the outpatient clinic of the Department of Vascular Medicine at regular intervals in which measurements of anti-Xa levels were performed. Dose adjustments were only done if peak anti-Xa activity was lower than 0.4 or higher than 1.2 anti-Xa units on repeated occasions. A multidisciplinary team of obstetricians and vascular medicine experts discussed patients at regular intervals. Women were advised to discontinue LMWH as soon as either contractions started, membranes ruptured or to administer the last injection the morning before the day that induction of labour or a caesarean section was planned. Women were also informed that epidural or spinal anaesthesia was contraindicated within 24 h after the last dose of LMWH. Management of postpartum haemorrhage was performed at the attending obstetrician's discretion.

Outcomes

The primary outcomes were PPH and severe PPH defined as the amount of blood loss estimated by the attending obstetrician or midwife of more than 500 ml and more than 1000 ml, respectively, within 24 h of

Table 1 Types of LMWH administered and the median and range of the doses per day

LMWH type	N	Median*	Range	Weight range
Enoxaparin, mg	16	120	60–200	53–116
Dalteparin, IU anti-Xa	9	15 000	10 000–20 000	64–115
Nadroparin, IU anti-Xa	64			
<75 kg	33	11 400	11 400–15 200	48–74
≥75 kg	31	15 200	11 400–20 900	75–117
Danaparoid, IU anti-Xa	3	4000	3000–4500	55–66
Tinzaparin, IU anti-Xa	3	18 000	14 000–28 000	75–82

*Doses are presented in milligrams for enoxaparin and IU for other low-molecular-weight heparins (LMWH).

delivery. Secondary outcomes were the estimated amount of blood loss in millilitres, blood transfusions in the first week postpartum, and recurrent VTE.

Statistical analysis

We calculated the incidence of PPH and severe PPH for LMWH users and non-users. Relative risks (RR) of PPH and severe PPH and their 95% CI in pregnant women treated with therapeutic doses of LMWH compared with non-users were calculated. Non-normally distributed data are presented as medians. We calculated the median blood loss difference between two cohorts of women and its 95% CI. Furthermore, we compared the median blood loss of both groups in strata of a priori defined other risk factors, if known (ie, type of vaginal delivery (normal vs assisted) or caesarean section (elective vs emergency), perineal laceration degree and ethnicity) to investigate their interaction with LMWH on the incidence of PPH. Blood transfusion in the first 24 h of delivery was compared between two groups of the study using the χ^2 test.

RESULTS

We identified 95 women who used therapeutic doses of LMWH during pregnancy for various indications (see figure 1 for case selection) and 524 women as a control cohort who did not use LMWH in their pregnancy. Baseline characteristics of the study groups are shown in table 2. Median gestational age (range) was 39 weeks (26–44) in LMWH users and 39 weeks (25–43) in non-users. In both cohorts, almost 93% of vaginal deliveries proceeded spontaneously (normal vaginal delivery) and 7% needed assistance. Almost a quarter (23%) of the women treated with LMWH delivered by caesarean section; half of these were elective, ie, planned before the onset of labour. In the control cohort 10% of the women underwent caesarean sections, most were emergency caesarean sections (90%).

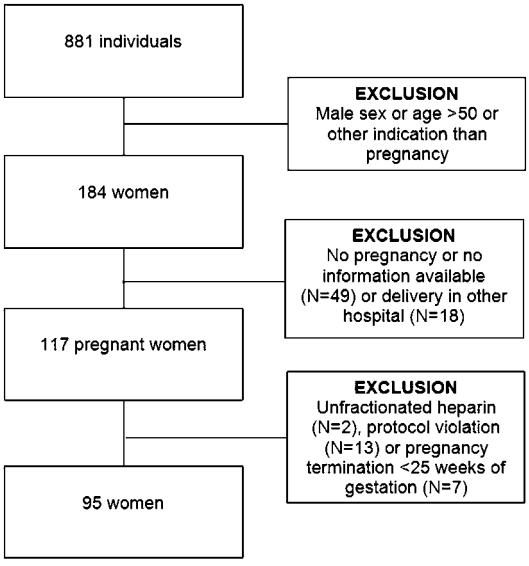

Figure 1 Inclusion flowchart of women treated with low-molecular-weight heparin.

Table 3 demonstrates the outcomes of the study, some stratified for types and subtypes of delivery. PPH occurred in 18% of women who used therapeutic doses of LMWH and in 22% of controls (RR for PPH 0.8; 95% CI 0.5 to 1.4). The incidence of severe PPH (6%) was the same in the two groups of LMWH users and non-users (RR for severe PPH 1.2; 95% CI 0.5 to 2.9). The risk of PPH and severe PPH after vaginal or caesarean section delivery was not statistically significantly different between the two groups of women.

Median blood loss after vaginal delivery was 250 ml (range 50–4000) and 300 ml (20–3600) ml in LMWH users and non-users, respectively (median difference −50; 95% CI −102 to 2). After caesarean section, it was 425 ml (200–2000) in LMWH users and 400 ml (100–2000) in non-users (25; −153 to 203). Median blood loss stratified for subtypes of delivery differed between LMWH users and non-users only after normal vaginal deliveries (200 ml (range 50–4000) and 300 ml (20–3600)) in LMWH users and non-users, respectively.

Median blood loss did not differ between groups after stratification for ethnicity and perineal laceration degree (data not shown).

Blood transfusion was given, at the discretion of the attending obstetrician, in 5% of LMWH users and 3% of non-users after delivery (OR 1.6; 95% CI 0.6 to 4.3).

In terms of efficacy, recurrent VTE was suspected in one woman (1.2%; 95% CI 0.6 to 5.8) despite the use of therapeutic doses of LMWH. However, a recurrent episode was not confirmed as ventilation/perfusion scintigraphy revealed a perfusion defect on the same localisation as the previous pulmonary embolism.

DISCUSSION

We observed that the incidence of severe bleeding during delivery was not increased by using therapeutic doses of LMWH during pregnancy, although a non-statistically significant increase in the risk of severe PPH was noticed.

Similar to our finding, a previous study reported no difference in the risk of PPH (5.7%) in women who delivered vaginally and used LMWH (doses not specified) and those who did not use LMWH (OR 1.0; 95% CI 0.2 to 4.7).[3] However, the absolute risk of PPH in our study cohorts (12% in LMWH users and 21% in non-LMWH users) was relatively higher. Although the incidence of PPH in our control group appears to be higher compared with other studies that assessed PPH in the general population,[17–19] a previously performed population-based cohort study in The Netherlands also observed an incidence of PPH of 19%.[4] An explanation could be the difference in blood loss estimation and in treatment regimens. In The Netherlands, an active management in the third stage of delivery (such as prophylactic administration of oxytocics, immediate cord clamping or controlled cord traction) is not

Table 2 Baseline characteristics of the two study groups

	Women who used therapeutic dose of LMWH (N=95)	Women who did not use LMWH (N=524)
Age, years median (range)	32 (21–43)	31 (18–44)
Ethnicity N (%)		
Caucasian	67 (70)	264 (50)
African	14 (15)	167 (32)
Others/unknown*	14 (15)	93 (18)
Gestational age, weeks median (range)	39 (26–44)	39 (25–43)
Delivery route		
Vaginal N (% of all women)	73 (77)	472 (90)
Normal delivery (% of vaginal deliveries)	67 (92)	437 (93)
Assisted delivery (% of vaginal deliveries)	6 (8)	35 (7)
Caesarean section N (% of all women)	22 (23)	52 (10)
Primary caesarean section (% of caesarean sections)	11 (50)	5 (10)
Emergency caesarean section (% of caesarean sections)	11 (50)	47 (90)
Perineal laceration degree N (% of vaginal deliveries)		
1st degree	7 (10)	43 (9)
2nd degree, episiotomy	12 (16)	59 (12)
2nd degree, spontaneous rupture	24 (33)	100 (22)
3rd degree	0 (0)	7 (1)
No laceration	29 (40)	263 (56)
Unknown	1 (1)	–
Birth weight, grams median (range)	3150 (365–4290)	3235 (555–5035)
Indication for LMWH administration N (% of all women)		
History of VTE	15 (16)	
History of VTE and thrombophilia	52 (55)	
Current VTE†	11 (12)	
Current VTE† and thrombophilia	2 (2)	
Recurrent thrombophlebitis and thrombophilia	1 (1)	
Antiphospholipid syndrome	4 (4)	
Pre-eclampsia	1 (1)	
Prosthetic heart valve	7 (7)	
Prosthetic heart valve + current heart thrombosis	1 (1)	
Current CVA	1 (1)	

*Data on ethnicity for two cases were missing.
†VTE during current pregnancy.
CVA, cerebrovascular accident; LMWH, low-molecular-weight heparin; VTE, venous thromboembolism.

Table 3 Incidence of PPH, severe PPH and median (range) of blood loss stratified for types of deliveries and blood transfusion rate in two groups of the study

	Women who used therapeutic doses of LMWH (N=95)	Women who did not use LMWH (N=524)	RR	Median difference	95% CI of RR or median difference
PPH events N (%)	17 (18)	113 (22)	0.8		0.5 to 1.4
Vaginal delivery	9 (12)	100 (21)	0.5		0.3 to 1.1
Caesarean section	8 (36)	13 (25)	1.7		0.6 to 5.0
Severe PPH events N (%)	6 (6)	29 (6)	1.2	–	0.5 to 2.9
Vaginal delivery	4 (5)	27 (6)	0.9		0.3 to 2.8
Caesarean section	2 (9)	2 (4)	2.5		0.3 to 18.9
Blood loss median (range)					
Vaginal delivery	250 (50–4000)	300 (20–3600)	–	−50	−102 to 2
Normal vaginal delivery	200 (50–4000)	300 (20–3600)	–	−100	−156 to −44
Assisted vaginal delivery	350 (250–550)	400 (100–2500)	–	−50	−217 to 117
Caesarean section	425 (200–2000)	400 (100–2000)	–	25	−153 to 203
Primary caesarean section	450 (200–1200)	200 (100–400)	–	250	−15 to 515
Emergency caesarean section	400 (200–2000)	400 (100–2000)	–	0	−225 to 225
Blood transfusion N (%)	5 (5)	18 (3)	1.6	–	0.6 to 4.3

LMWH, low-molecular-weight heparin; PPH, postpartum haemorrhage.

routinely performed, although oxytocics administered in the third stage of delivery have been shown to reduce the amount of blood loss.[20] Therefore, we hypothesise that withholding oxytocics might have led to a higher incidence of PPH in our control cohort, whereas this was not observed in the treated women because LMWH use warranted an active management of the third stage of delivery according to the hospital protocol. Furthermore, as our hospital is a tertiary referral centre, the observed high incidence of blood loss more than 500 ml in the control cohort may be explained by comorbidities that increase the risk of a complicated delivery.

For caesarian section, the incidence of severe PPH may be more relevant to evaluate because blood loss between 500 and 1000 ml is not considered uncommon during surgery. Severe PPH risk was 2.5 times higher (95% CI 0.3 to 18.9) in women who used LMWH compared with those who did not, although the certainty of this estimate is limited by the small number of individuals in this stratum. In another study in which the doses of the administered LMWH was not specified, the risk of severe PPH for LMWH users (5%) in caesarean sections was surprisingly stated as half of the controls (12.5%) (OR 0.4; 95% CI 0.04 to 3.4).[3]

Although this is the largest cohort of pregnancies treated with high doses of LMWH, its power to calculate the risk of PPH is limited and is at most 44% in calculating the RR of PPH in vaginal deliveries. Therefore, we compared the median of blood loss between cohorts of LMWH users and non-users considering that the median is less sensitive to outliers. The only difference in median blood loss was found in the subgroup of normal vaginal deliveries in which it was lower in the LMWH users.

Some issues warrant comment. First, although this was a controlled cohort study, it is likely that strategies to decrease the risk of PPH differed between women who were treated with LMWH and controls. Given the observational study design, our study does not exclude an increased risk of PPH by the use of therapeutic LMWH if similar obstetric measures are taken. Second, we have not measured anti-Xa levels shortly before delivery, as this was not part of the hospital protocol. However, the advice given to all women reflects a real-life situation (ie, to discontinue LMWH when contractions started, membranes ruptured or the evening before the planned induction of labour or caesarean section). Furthermore, evidence about the association between this duration and the risk of PPH is conflicting.[8 9 21] Third, blood loss was estimated rather than measured, which may have led to higher estimates.[22] This was done similarly in women treated and untreated with LMWH. If anything, it is more likely that blood loss would be overestimated rather than underestimated in women who used LMWH than in women without LMWH.

In conclusion, we observed that therapeutic doses of LMWH administered in pregnancy was not associated with clinically meaningful increase in the incidence of PPH or severe PPH in women who delivered in our hospital. Although this observation may be confounded by the differential use of strategies to prevent bleeding, it is unlikely that LMWH levels in blood at the time of delivery can cause PPH knowing the routine recommendations to stop the injections when signs of labour start. A randomised controlled trial to assess the safety of therapeutic doses of LMWH to prevent VTE in pregnant women is necessary to provide a definite answer about the optimal dose of LMWH in this population.

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Competing interests None.

Ethics approval This study was approved by the Medical Ethics Committee of the Academic Medical Center in Amsterdam.

Contributors SR and DMC and ACS collected the data. SR and DMC performed the analysis and contributed equally to the paper. SR, DMC and SM designed the study and wrote the manuscript. ACS, HW, JAMvdP, HRB, PWK and SM critically reviewed the paper and discussed the analysis. All authors approved the final version.

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