Thrombophilia ad dies vitae

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Chapter 10

Risk of postpartum haemorrhage in women receiving therapeutic doses of low-molecular-weight heparin

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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 to prevent thrombosis while avoiding bleeding complications is unclear. We investigated whether use of therapeutic doses of LMWH increases the risk of postpartum haemorrhage (PPH).

Methods

We identified all pregnant women who received therapeutic doses of LMWH between 1995 and 2008 in the Academic Medical Centre, Amsterdam, The Netherlands. We compared the risk of PPH and estimated amount of blood loss in 83 women treated with LMWH to 523 pregnant women who did not use LMWH.

Results

PPH risk after vaginal delivery was 12% (7/83) in LMWH users and 21% (97/523) in non-users (RR 0.6; 95%CI 0.3 to 1.2). After caesarean section, PPH risk was 9% (2/22) in LMWH users and 4% (2/51) in non-users (RR 2.3; 0.3 to 17). Median amount of blood loss in vaginal deliveries was 200 mL in LMWH users and 300 mL in non-users, (difference 100 mL; 41 to 159). In caesarean sections the median blood loss did not differ between LMWH users and non-users (425 and 400 mL respectively, difference 25 mL; -133 to 183). In emergency caesarean sections this was higher in LMWH users than in non-users (450 and 200 mL respectively, difference 250 mL; 9 to 491).

Conclusion

Therapeutic doses of LMWH are relative safe to use for pregnant women who deliver in the hospital setting of optimal obstetric care. An increased risk of bleeding appears to occur in the setting of emergency caesarean section.

Introduction

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 one crucial disadvantage, as its anticoagulant effect can only be partially antagonized. This is of particular importance with respect to its use in high doses and raises concerns about an increased risk of postpartum haemorrhage (PPH) when used in pregnant women.

PPH is defined by the World Health Organization (WHO) as postpartum blood loss in excess of 500 mL.[2] However, other definitions have been suggested, such as the addition of blood loss exceeding 1000 mL following caesarean section.[3] PPH has an incidence of 19% in nulliparous deliveries in the Netherlands.[4] The diagnosis encompasses excessive blood loss from uterus, cervix, vagina and perineum. The commonest cause of primary PPH (PPH < 24 hours following delivery) is lack of efficient uterine contraction (uterine atony).[5]

In order to limit the risk of PPH, current guidelines recommend discontinuation of LMWH 12 to 24 hours prior to delivery.[1;6] However, as labour can commence spontaneously, timely discontinuation cannot be guaranteed. The risk of PPH associated with use of therapeutic doses of LMWH has been assessed in few studies.[3;7-12] 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;8;10] Three studies assessed bleeding risk in pregnant women (including those who were treated with therapeutic doses of LMWH).[3;11;12] However, only one study reports the bleeding risk associated with antepartum therapeutic doses of LMWH.[11] In this prospective multicentre survey in the UK and Ireland, blood loss > 500 mL occurred in 6/126 (4.8%) women who were treated with therapeutic doses of LMWH. The two other studies also assessed PPH associated with LMWH, however the bleeding rate associated with therapeutic doses only can not be deduced from these papers.[3;12]

In our hospital all pregnant women whom 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.[13] 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 7 of 8 recurrent episodes of VTE occurred in women on prophylactic or intermediate doses of enoxaparin.[14]

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

Methods

Identification of study cohorts

Women who had used therapeutic doses of LMWH during pregnancy were identified by collection of all 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 Centre (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. Cases 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.

Intervention

LMWH was dosed on body weight prior to pregnancy, according to the hospital's protocol. Measurements of anti-Xa levels were performed in all women who used LMWH during their regular visits to the outpatient clinic of the Department of Vascular Medicine. Dose-adjustments were only performed 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 with regular intervals. Women were advised to discontinue LMWH as soon as either contractions started, membranes ruptured or the evening before the induction of labour or a caesarean section was planned.

Outcomes

The primary outcome was PPH, defined as blood loss > 500 mL following vaginal delivery or >1000 mL following caesarean section within 24 hours of delivery. Secondary outcomes were the estimated amount of blood loss in mL, blood transfusions in the first week postpartum, and recurrent VTE.

Statistical analysis

We calculated the absolute risk of PPH and its 95% confidence interval (95%CI) for both groups of LMWH users and non-users. Subsequently relative risk (RR) of PPH and 95%CI in pregnant women treated with therapeutic doses of LMWH compared to non-users was calculated. Non-normally distributed data are presented as medians. We calculated the median blood loss difference and its 95%CI between the two groups of women. The difference of median blood loss between groups was evaluated by Mann-Whitney test.

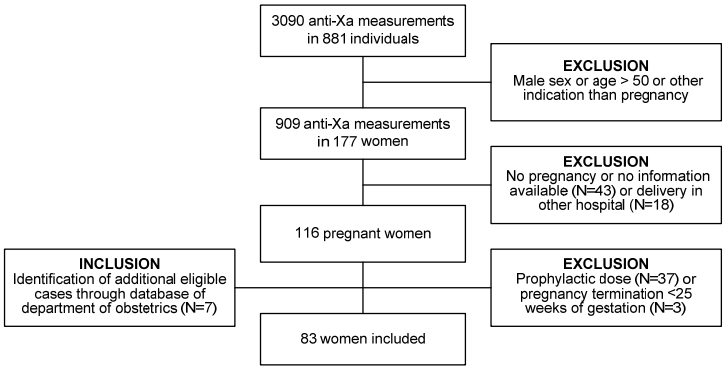
Furthermore, we compared the median blood loss of both groups in strata of a priori defined other risk factors (i.e. type of vaginal delivery [normal versus assisted] or caesarean section [emergency versus primary] and ethnicity) to investigate their interaction with LMWH on PPH risk. Blood transfusion in the first 24 hours of delivery was compared between two groups of the study using the χ^2 test.

Results

We identified 83 women who used therapeutic doses of LMWH during pregnancy for various indications (see Flowchart for case selection).

Baseline characteristics of the study groups are shown in Table 1. Mean gestational age (±SD) was 39±3 weeks in LMWH users and 38±4 in non-users. In both cohorts, 93% of vaginal deliveries proceeded spontaneously (normal vaginal delivery) and 7% needed assistance. Almost one-quarter (27%) of the women treated with LMWH delivered by caesarean sections; half of these were planned before onset of labour (primary caesarean section). In the control cohort only 10% of the women underwent caesarean sections, most were emergency caesarean sections.

Inclusion flowchart of women treated with LMWH



PPH occurred in 11% of the women who used therapeutic doses of LMWH and in 19% of the controls (RR for PPH: 0.6; 95%CI 0.3 to 1.1) (Table 2).The absolute risks of PPH in women using LMWH were within the same range after vaginal delivery (12%) and after caesarean section (9%). However, in the control cohort these risks were 21% and 4% respectively (RR for PPH after vaginal delivery 0.6; 95%CI 0.3 to 1.2; RR after caesarean section 2.3; 95%CI 0.3 to 17).

Table 1. Baseline characteristics of two study groups

	Women who used therapeutic dose of LMWH (N=83)	Women who did not use LMWH (N=523)
Age, years Mean± SD	32±5	31±5
Ethnicity N (%)		
Caucasian	59 (71)	263 (50)
African	11 (13)	167 (32)
Others/unknown	13 (16)	93 (18)
Gestational age, weeks Mean± SD	39±3	38±4
Delivery route		
Vaginal N (% of all women)	61 (73)	472 (90)
Normal delivery, (% of vaginal deliveries)	57 (93)	437 (93)
Assisted delivery, (% of vaginal deliveries)	4 (7)	35 (7)
Caesarean section N (% of all women)	22 (27)	51 (10)
Primary caesarean section, (% of caesarean sections)	11 (50)	5 (10)
Emergency caesarean section, (% of caesarean sections)	11 (50)	46 (90)
Perineal laceration degree N (% of vaginal deliveries)		
1st degree	4 (7)	43 (9)
2nd degree, Episiotomy	10 (16)	59 (12)
2nd degree, Spontaneous rupture	22 (36)	100 (22)
3rd degree	0 (0)	7 (1)
No laceration	24 (39)	263 (56)
Unknown	1 (2)	-
Birth weight, grams Mean± SD	3044±736	3053±885
Indication for LMWH administration N (% of all women)		
History of VTE	14 (17)	
History of VTE and thrombophilia	46 (55)	
Current VTE*	11 (13)	
Current VTE* and thrombophilia	2 (3)	
Antiphospholipid syndrome	2 (3)	
Pre-eclampsia	1 (1)	
Prosthetic heart valve	5 (6)	
Prostatic heart valve+ current heart thrombosis	1 (1)	
Current CVA	1 (1)	

LMWH=low-molecular -weight heparin, VTE= venous thromboembolism. * VTE during current pregnancy

Median blood loss after vaginal delivery was 200 (range, 50 to 4000) and 300 (20 to 3600) mL in LMWH users and non-users respectively (median difference 100; 95%CI: 41 to 159). Blood loss did not differ between the groups after stratification for delivery subtypes (i.e. normal or assisted vaginal delivery, and primary or emergency caesarean section), ethnicity and perineal laceration degree (data not shown), except for the stratum of no-laceration (intact perineum) where the median of estimated blood loss (range) was 175 (50 to 1600) in cases and 300 (50 to 3500) in controls with median difference of 125; 95% CI 87 to 213.
Blood transfusion was given as judged by the attending obstetrician in 5% of LMWH users and 3% of non-users after delivery (OR 1.4; 95%CI: 0.5 to 4.3).
In terms of efficacy, recurrent VTE was suspected in one woman (1.2%, 95%CI 0.6-5.8) despite the use of therapeutic doses of LMWH. However, a recurrent episode was not established as ventilation/perfusion scintigraphy revealed a perfusion defect on the same localization of the previous PE.

Table 2. Risk of PPH, median and range of blood loss, stratified for subtypes of deliveries in women with and without therapeutic doses of LMWH

	Women who used therapeutic doses of LMWH (N=83)	Women who did not use LMWH (N=523)	RR / Median difference	95%CI
PPH events N (%)	9 (11)	99 (19)	0.6*	0.3 to 1.1
Vaginal delivery	7 (12)	97 (21)	0.6*	0.3 to 1.2
Caesarean section	2 (9)	2 (4)	2.3*	0.3 to 17
Blood loss Median (range)				
Vaginal delivery	200 (50 to 4000)	300 (20 to 3600)	-100+	41 to 159
Normal vaginal delivery	200 (50 to 4000)	300 (20 to 3600)	-100+	39 to 161
Assisted vaginal delivery	400 (250 to 550)	400 (100 to 2500)	0+	-772 to 772
Caesarean section	425 (200 to 2000)	400 (100 to 2000)	25+	-133 to 183
Primary caesarean section	400 (200 to 2000)	400 (100 to 2000)	0+	-225 to 225
Emergency caesarean section	450 (200 to 1200)	200 (100 to 400)	250+	9 to 491
Blood transfusion N (%)	4 (5)	18 (3)	1.4*	0.5 to 4.3

PPH= postpartum haemorrhage (>500 mL blood loss in vaginal delivery and >1000 mL blood loss in caesarean section), LMWH= low-molecular-weight heparin. Blood loss is reported in mL. * depicts relative risk (RR) and + depicts median difference.

Discussion

We observed that in vaginal deliveries the risk of PPH was not increased in women who used therapeutic doses of LMWH compared with those who did not. The upper limit of the 95% CI is compatible with only a 10% increase and corresponds with 160 mL of blood loss in vaginal deliveries. This finding is in line with a previous study that reported similar risks (5.7%) of PPH in vaginal deliveries in women who 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 both our study groups (12% in LMWH users and 21% in non-LMWH users) was higher. Although the PPH rate in our control group appears high as compared to other studies that assessed PPH in general populations,[15-17] a previously performed population-based cohort in the Netherlands showed a comparable PPH incidence of 19% (PPH defined as blood loss >500 mL).[4] An explanation for this high incidence could be the difference in blood loss estimation and in treatment regimens. In the Netherlands, an active management during the third stage of delivery (such as prophylactic administration of oxytocics, immediate cord clamping or controlled cord traction) is not routinely performed. Oxytocics administered in the third stage of delivery have previously been shown to reduce the amount of blood loss.[18] Therefore we assume that withholding oxytocics might have led to a higher incidence of PPH in our control cohort, whereas this was not observed in the cases since LMWH use warranted an active management of the third stage of delivery. Furthermore, as our hospital is a tertiary referral centre, the observed high incidence of blood loss >500 mL in the control cohort may be explained by comorbidities that increase the risk of a complicated delivery.

In caesarean sections, PPH risk was 2.3 times higher (95%CI: 0.3 to 17) in women who used LMWH as compared to those who did not, although the certainty of this estimate is limited by the small number of patients. In another study, the risk of PPH for LMWH users (5%) in caesarean sections was half of the controls (12.5%) (OR 0.4; 95%CI: 0.04 to 3.4).[3] We were not able to calculate the risk of PPH in two subtypes of caesarean sections because of few PPH events; 2 in cases (one underwent emergency and one primary caesarean section) and 2 in controls (both had emergency caesarean section). In primary caesarean sections, the amount of blood loss was not different between LMWH users and non-users.

The main limitation of this cohort study is its retrospective design. We were unable to retrieve the anti-Xa level shortly prior to delivery and the time interval between LMWH cessation and delivery. However, evidence about the association between this duration and the risk of PPH is conflicting.[8;9;19]

In conclusion, therapeutic doses of LMWH are relatively safe to use in women who deliver vaginally in the hospital setting of optimal obstetric care. However an increased risk of bleeding in the setting of emergency caesarean section can not be excluded.

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