Incidence of postpartum hemorrhage in women receiving therapeutic doses of low-molecular-weight heparin

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000257
Article Type:	Research
Date Submitted by the Author:	17-Jul-2011
Complete List of Authors:	Roshani, Sara; Leiden University Medical Center, Department of Clinical Epidemiology Cohn, Danny; Academic Medical Center, Amsterdam, Department of Vascular Medicine Stehouwer, Alexander; Academic Medical Center, Amsterdam, Department of Vascular Medicine Wolf, Hans; Academic Medical Center, Amsterdam, Department of Obstetrics and Gynecology van der Post, Joris; Academic Medical Center, Amsterdam, Department of Obstetrics and Gynecology Büller, Harry; Academic Medical Center, Amsterdam, Department of Vascular Medicine Kamphuisen, Pieter; Academic Medical Center, Amsterdam, Department of Vascular Medicine Middeldorp, Saskia; Academic Medical Center, Amsterdam, Department of Vascular Medicine
Primary Subject Heading:	Haematology
Keywords:	venous thromboembolism, Low-molecular-weight heparin, postpartum hemorrhage

Incidence of postpartum hemorrhage in women receiving therapeutic doses of low-molecular-weight heparin

Sara Roshani [a,b], Danny M. Cohn [a], Alexander C. Stehouwer [a], Hans Wolf [c], Joris A. M. van der Post [c], Harry R. Büller [a], Pieter W. Kamphuisen [a], Saskia Middeldorp [a]

Authors' affiliations

[a]Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

[b]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

[c]Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam, The Netherlands

Correspondence: Saskia Middeldorp, Department of Vascular Medicine, Academic Medical Center, F4-276, Meibergdreef 9, 1105 AZ Amsterdam, Phone: +31 (0)20 5665976, Fax: +31 (0)20 6968833, E-mail: s.middeldorp@amc.uva.nl

Keywords: Low-molecular-weight heparin, postpartum hemorrhage, venous thromboembolism

Word count: 2112

Article focus:

- To compare the incidence of postpartum hemorrhage (PPH) (i.e. blood loss> 500 mL in the first 24 hours 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 sever 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 was not associated with 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
- 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

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. We investigated whether therapeutic doses of LMWH increase the incidence of postpartum hemorrhage in a retrospective controlled cohort study.

Methods:

We identified all pregnant women who received therapeutic doses of LMWH between 1995 and 2008 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. We compared the incidence of PPH (blood loss> 500 mL), incidence of severe PPH (blood loss> 1000 mL) and the median blood loss 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). 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:

We observed that therapeutic doses of LMWH in pregnancy was not associated with clinically meaningful increase in the incidence of PPH or severe PPH in women delivered in our hospital although this observation may be confounded by differential

use of strategies to prevent bleeding. A randomized controlled trial is necessary to provide a definite answer about the optimal dose of LMWH in pregnancy.

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 the disadvantage that 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 bleeding, most notably postpartum hemorrhage (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, since 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 uterus, cervix, vagina and perineum. The commonest cause of primary PPH (PPH < 24 hours following delivery) is 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 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 multicenter 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 6/126 (4.8%) and 3/174 (1.7%) of women who were treated with therapeutic doses of LMWH in these 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 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.[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 7 of 8 recurrent episodes of VTE occurred in women on prophylactic or intermediate doses of enoxaparin.[16]

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

Material and methods

Identification of study cohorts

By hospital protocol, anti-Xa levels were measured at one-month intervals in women who were treated with therapeutic doses of LMWH during pregnancy. Thus, our study cohort was identified by 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.

Intervention

The hospital protocol was to base LMWH doses on body weight prior to 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 with 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 the evening before the induction of labour or a cesarean section was planned. Also women were informed that epidural or spinal anesthesia was contraindicated within 24 hours after the last dose of LMWH. Management of postpartum hemorrhage 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 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 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 to 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 (i.e. type of vaginal delivery [normal versus assisted] or cesarean section [elective versus emergency], perineal laceration degree and ethnicity) to investigate their interaction with LMWH on the incidence of PPH. Blood transfusion in the first 24 hours of delivery was compared between two groups of the study using the X^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 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 (26-44) weeks in LMWH users and 39 (25-43) in non-users. In both cohorts, almost 93% of vaginal deliveries proceeded spontaneously (normal vaginal delivery) and 7% needed assistance. Almost one-quarter (23 %) of the women treated with LMWH delivered by cesarean sections; half of these were elective, i.e. planned before onset of labour. In the control cohort 10% of the women underwent cesarean sections, most were emergency cesarean sections (90%).

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 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 cesarean section delivery was not statistically significant different between two groups of women.

Median blood loss after vaginal delivery was 250 (range, 50 to 4000) and 300 (20 to 3600) mL in LMWH users and non-users respectively (median difference -50; 95%CI: -102 to 2). After cesarean section, it was 425 (200 to 2000) mL in LMWH users and 400 (100 to 2000) mL 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 (range, 50 to 4000) and 300 (20 to 3600) mL 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 0.6-5.8) 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 localization as the previous PE.

Discussion

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

Similar to our finding a previous study 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 our both 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 high as compared to 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 during the third stage of delivery (such as prophylactic administration of oxytocics, immediate cord clamping or controlled cord traction) is not routinely performed, although oxytocics administered in the third stage of delivery have been shown to reduce the amount of blood loss.[20] Therefore we hypothesize 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 since 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 center, 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 cesarian section, the incidence of severe PPH may be more relevant to evaluate since 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 as compared to those who did not, although the certainty of this estimate is limited by the small number of individuals in this stratum. In another study where the doses of the administered LMWH was not specified, the risk of severe PPH for LMWH users (5%) in cesarean sections was surprisingly stated 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 in subtypes of vaginal deliveries and cesarean sections is still limited. Therefore we compared the median of blood loss between cohorts of LMWH users and non-users considering that median is less sensitive to outliers. The only difference in median blood loss was found in the subgroup of normal vaginal deliveries where 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 use of therapeutic LMWH if similar obstetric measures are taken. Second, we have not measured anti-Xa levels shortly prior to delivery, since this was not part of the hospital protocol. However, the advice given to all women reflects a real life situation (i.e. to discontinue LMWH when contractions started, membranes ruptured or the evening before the planned induction of labour or cesarean 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 lead to higher estimates.[22] This was done similarly in women treated and untreated with LMWH. If any, it is more likely to overestimate rather than underestimate blood loss 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 differential use of strategies to prevent bleeding. A randomized controlled trial to assess the safety of therapeutic doses of LMWH to prevent venous thromboembolism in pregnant women is necessary to provide a definite answer about the optimal dose of LMWH in this population.

Acknowledgements

The authors would like to thank Miss Sofie Hamers, medical student, for assisting us with data collection. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Disclosures

Harry Büller has received honoraria and research support from GlaxoSmithKline and pfizer. Pieter W. Kamphuisen has received honoraria from GlaxoSmithKline and LeoPharma. Saskia Middeldorp has received honoraria and research support from GlaxoSmithKline.

Addendum

S. Roshani and D.M. Cohn performed the data analysis and wrote the manuscript. These author contributed equally to this paper. A.C. Stehouwer contributed in collecting the patients´ information. H. Wolf, J.A. M. van der Post , H.R. Büller , P.W. Kamphuisen and S.Middeldorp critically reviewed the paper and discussed the data analysis.

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 to 200	53 to 116
Dalteparin, IU anti-Xa	9	15000	10000 to 20000	64 to 115
Nadroparin, IU anti-Xa	64			
<75 kg	33	11400	11400 to 15200	48 to 74
≥75 kg	31	15200	11400 to 20900	75 to 117
Danaparoid, IU anti-Xa	3	4000	3000 to 4500	55 to 66
Tinzaparin, IU anti-Xa	3	18000	14000 to 28000	75 to 82

* Doses are presented in mg for enoxaparin and IU for other LMWHs

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)
Cesarean section N (% of all women)	22 (23)	52 (10)
Primary cesarean section, (% of cesarean sections)	11 (50)	5 (10)
Emergency cesarean section, (% of cesarean 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)	
Prostatic heart valve+ current heart thrombosis	1 (1)	
Current CVA	1 (1)	

*Data on ethnicity for 2 cases was missing

†VTE during current pregnancy

.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
Cesarean 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
Cesarean section	2 (9)	2 (4)	2.5		0.3 to 18.9
Blood loss Median (range)					
Vaginal delivery	250 (50 to 4000)	300 (20 to 3600)	-	-50	-102 to 2
Normal vaginal delivery	200 (50 to 4000)	300 (20 to 3600)	-	-100	-156 to -44
Assisted vaginal delivery	350 (250 to 550)	400 (100 to 2500)	-	-50	-217 to 117
Cesarean section	425 (200 to 2000)	400 (100 to 2000)	-	25	-153 to 203
Primary cesarean section	450 (200 to 1200)	200 (100 to 400)	-	250	-15 to 515
Emergency cesarean section	400 (200 to 2000)	400 (100 to 2000)	-	0	-225 to 225
Blood transfusion N (%)	5 (5)	18 (3)	1.6	-	0. 6 to 4.3

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

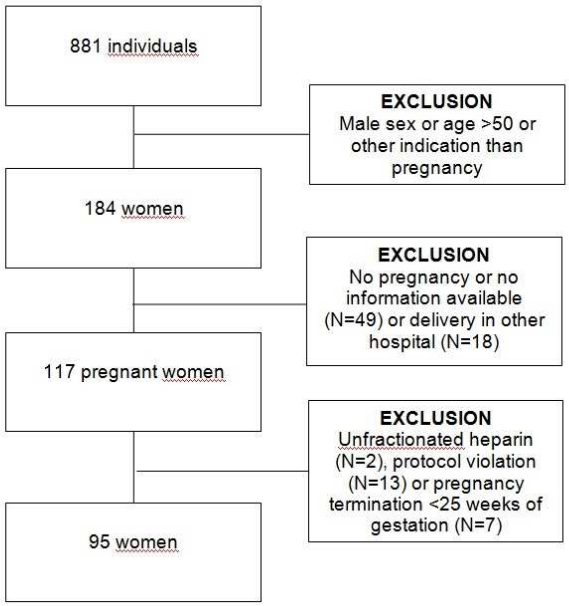
	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	6-13
		(c) Consider use of a flow diagram	13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	8-9-16

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Figure 1. Inclusion flowchart of women treated with LMWH



266x189mm (96 x 96 DPI)

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000257.R1
Article Type:	Research
Date Submitted by the Author:	22-Aug-2011
Complete List of Authors:	Roshani, Sara; Academic Medical Center, Amsterdam, Department of Vascular Medicine; Leiden University Medical Center, Department of Clinical Epidemiology Cohn, Danny; Academic Medical Center, Amsterdam, Department of Vascular Medicine Stehouwer, Alexander; Academic Medical Center, Amsterdam, Department of Vascular Medicine Wolf, Hans; Academic Medical Center, Amsterdam, Department of Obstetrics and Gynecology van der Post, Joris; Academic Medical Center, Amsterdam, Department of Obstetrics and Gynecology Büller, Harry; Academic Medical Center, Amsterdam, Department of Vascular Medicine Kamphuisen, Pieter; Academic Medical Center, Amsterdam, Department of Vascular Medicine Middeldorp, Saskia; Academic Medical Center, Amsterdam, Department of Vascular Medicine
Primary Subject Heading:	Haematology
Keywords:	venous thromboembolism, Low-molecular-weight heparin, postpartum hemorrhage

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

Sara Roshani [a,b], Danny M. Cohn [a], Alexander C. Stehouwer [a], Hans Wolf [c], Joris A. M. van der Post [c], Harry R. Büller [a], Pieter W. Kamphuisen [a], Saskia Middeldorp [a]

Authors' affiliations

[a]Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

[b]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

[c]Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam, The Netherlands

Correspondence: Saskia Middeldorp, Department of Vascular Medicine, Academic Medical Center, F4-276, Meibergdreef 9, 1105 AZ Amsterdam, Phone: +31 (0)20 5665976, Fax: +31 (0)20 6968833, E-mail: s.middeldorp@amc.uva.nl

Keywords: Low-molecular-weight heparin, postpartum hemorrhage, venous thromboembolism

Word count: 2112

Article focus:

- To compare the incidence of postpartum hemorrhage (PPH) (i.e. blood loss> 500 mL in the first 24 hours 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 sever 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 was not associated with 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
- 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

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. We investigated whether therapeutic doses of LMWH increase the incidence of postpartum hemorrhage in a retrospective controlled cohort study.

Methods:

We identified all pregnant women who received therapeutic doses of LMWH between 1995 and 2008 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. We compared the incidence of PPH (blood loss> 500 mL), incidence of severe PPH (blood loss> 1000 mL) and the median blood loss 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). 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:

We observed that therapeutic doses of LMWH in pregnancy was not associated with clinically meaningful increase in the incidence of PPH or severe PPH in women delivered in our hospital although this observation may be confounded by differential

use of strategies to prevent bleeding. A randomized controlled trial is necessary to provide a definite answer about the optimal dose of LMWH in pregnancy.

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 the disadvantage that 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 bleeding, most notably postpartum hemorrhage (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, since 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 uterus, cervix, vagina and perineum. The commonest cause of primary PPH (PPH < 24 hours following delivery) is 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 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 multicenter 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 6/126 (4.8%) and 3/174 (1.7%) of women who were treated with therapeutic doses of LMWH in these 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 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.[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 7 of 8 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.

Material and methods

Identification of study cohorts

By hospital protocol, anti-Xa levels were measured at one-month intervals in women who were treated with therapeutic doses of LMWH or heparinoid during pregnancy. Thus, our study cohort was identified by 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 prior to 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 with 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 the evening before the induction of labour or a cesarean section was planned. Also women were informed that epidural or spinal anesthesia was contraindicated within 24 hours after the last dose of LMWH. Management of postpartum hemorrhage 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 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 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 to 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 (i.e. type of vaginal delivery [normal versus assisted] or cesarean section [elective versus emergency], perineal laceration degree and ethnicity) to investigate their interaction with LMWH on the incidence of PPH. Blood transfusion in

the first 24 hours of delivery was compared between two groups of the study using the X^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 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 (26-44) weeks in LMWH users and 39 (25-43) in non-users. In both cohorts, almost 93% of vaginal deliveries proceeded spontaneously (normal vaginal delivery) and 7% needed assistance. Almost one-quarter (23 %) of the women treated with LMWH delivered by cesarean sections; half of these were elective, i.e. planned before onset of labour. In the control cohort 10% of the women underwent cesarean sections, most were emergency cesarean sections (90%).

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 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 cesarean section delivery was not statistically significant different between two groups of women.

Median blood loss after vaginal delivery was 250 (range, 50 to 4000) and 300 (20 to 3600) mL in LMWH users and non-users respectively (median difference -50; 95%CI: -102 to 2). After cesarean section, it was 425 (200 to 2000) mL in LMWH users and 400 (100 to 2000) mL 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 (range, 50 to 4000) and 300 (20 to 3600) mL 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 0.6-5.8) 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 localization as the previous PE.

Discussion

We observed that the incidence of severe bleeding during delivery was not increased by using therapeutic doses of LMWH during pregnancy, though 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 high as compared to 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 during the third stage of delivery (such as prophylactic administration of oxytocics, immediate cord clamping or controlled cord traction) was not routinely performed, although oxytocics administered in the third stage of delivery have been shown to reduce the amount of blood loss.[20] Therefore we hypothesize 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 since 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 center, 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 cesarian section, the incidence of severe PPH may be more relevant to evaluate since 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 as compared to those who did not, although the certainty of this estimate is limited by the small number of individuals in this stratum. In another study where the doses of the administered LMWH was not specified, the risk of severe PPH for LMWH users (5%) in cesarean sections was surprisingly stated 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 still limited and was at most 44% in calculating the relative risk of PPH in vaginal deliveries. Therefore we compared the median of blood loss between cohorts of LMWH users and non-users considering that median is less sensitive to outliers. The only difference in median blood loss was found in the subgroup of normal vaginal deliveries where 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 use of therapeutic LMWH if similar obstetric measures are taken. Second, we have not measured anti-Xa levels shortly prior to delivery, since this was not part of the hospital protocol. However, the advice given to all women reflects a real life situation (i.e. to discontinue LMWH when contractions started, membranes ruptured or the evening before the planned induction of labour or cesarean 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 lead to higher estimates.[22] This was done similarly in women treated and untreated with LMWH. If any, it is more likely to overestimate rather than underestimate blood loss 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 differential use of strategies to prevent bleeding, it is unlikely that LMWH levels at the time of delivery can cause PPH knowing the routine recommendations to stop the injections when signs of labor start. A randomized controlled trial to assess the safety of therapeutic doses of LMWH to prevent venous thromboembolism in pregnant women is necessary to provide a definite answer about the optimal dose of LMWH in this population.

Acknowledgements

The authors would like to thank Miss Sofie Hamers, medical student, for assisting us with data collection. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Disclosures

Harry Büller has received honoraria and research support from GlaxoSmithKline and pfizer. Pieter W. Kamphuisen has received honoraria from GlaxoSmithKline and LeoPharma. Saskia Middeldorp has received honoraria and research support from GlaxoSmithKline.

Addendum

S. Roshani and D.M. Cohn performed the data analysis and wrote the manuscript. These author contributed equally to this paper. A.C. Stehouwer contributed in collecting the patients´ information. H. Wolf, J.A. M. van der Post , H.R. Büller , P.W. Kamphuisen and S.Middeldorp critically reviewed the paper and discussed the data analysis.

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 to 200	53 to 116
Dalteparin, IU anti-Xa	9	15000	10000 to 20000	64 to 115
Nadroparin, IU anti-Xa	64			
<75 kg	33	11400	11400 to 15200	48 to 74
≥75 kg	31	15200	11400 to 20900	75 to 117
Danaparoid, IU anti-Xa	3	4000	3000 to 4500	55 to 66
Tinzaparin, IU anti-Xa	3	18000	14000 to 28000	75 to 82

* Doses are presented in mg for enoxaparin and IU for other LMWHs

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)
Cesarean section N (% of all women)	22 (23)	52 (10)
Primary cesarean section, (% of cesarean sections)	11 (50)	5 (10)
Emergency cesarean section, (% of cesarean 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 2 cases was missing, †VTE during current pregnancy

.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
Cesarean 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
Cesarean section	2 (9)	2 (4)	2.5		0.3 to 18.9
Blood loss Median (range)					
Vaginal delivery	250 (50 to 4000)	300 (20 to 3600)	-	-50	-102 to 2
Normal vaginal delivery	200 (50 to 4000)	300 (20 to 3600)	-	-100	-156 to -44
Assisted vaginal delivery	350 (250 to 550)	400 (100 to 2500)	-	-50	-217 to 117
Cesarean section	425 (200 to 2000)	400 (100 to 2000)	-	25	-153 to 203
Primary cesarean section	450 (200 to 1200)	200 (100 to 400)	-	250	-15 to 515
Emergency cesarean section	400 (200 to 2000)	400 (100 to 2000)	-	0	-225 to 225
Blood transfusion N (%)	5 (5)	18 (3)	1.6	-	0. 6 to 4.3

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

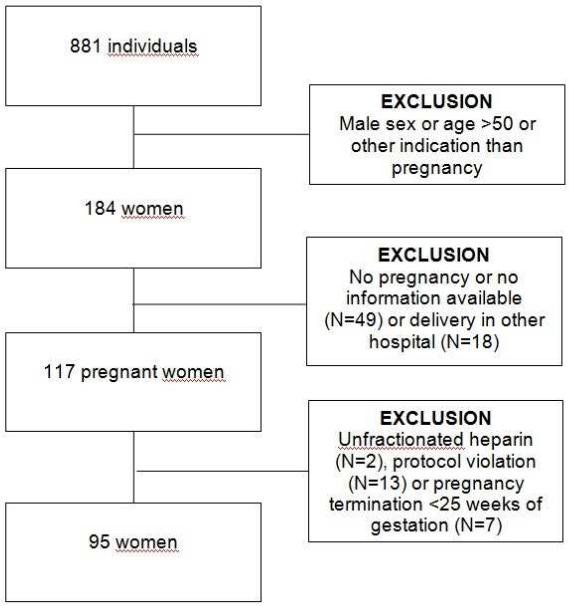
	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	6-13
		(c) Consider use of a flow diagram	13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	8-9-16

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Figure 1. Inclusion flowchart of women treated with LMWH



266x189mm (96 x 96 DPI)

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2011-000257.R2
Article Type:	Research
Date Submitted by the Author:	25-Sep-2011
Complete List of Authors:	Roshani, Sara; Academic Medical Center, Amsterdam, Department of Vascular Medicine; Leiden University Medical Center, Department of Clinical Epidemiology Cohn, Danny; Academic Medical Center, Amsterdam, Department of Vascular Medicine Stehouwer, Alexander; Academic Medical Center, Amsterdam, Department of Vascular Medicine Wolf, Hans; Academic Medical Center, Amsterdam, Department of Obstetrics and Gynecology van der Post, Joris; Academic Medical Center, Amsterdam, Department of Obstetrics and Gynecology Büller, Harry; Academic Medical Center, Amsterdam, Department of Vascular Medicine Kamphuisen, Pieter; Academic Medical Center, Amsterdam, Department of Vascular Medicine Middeldorp, Saskia; Academic Medical Center, Amsterdam, Department of Vascular Medicine
Primary Subject Heading:	Haematology
Secondary Subject Heading:	
Keywords:	venous thromboembolism, Low-molecular-weight heparin, postpartum hemorrhage

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

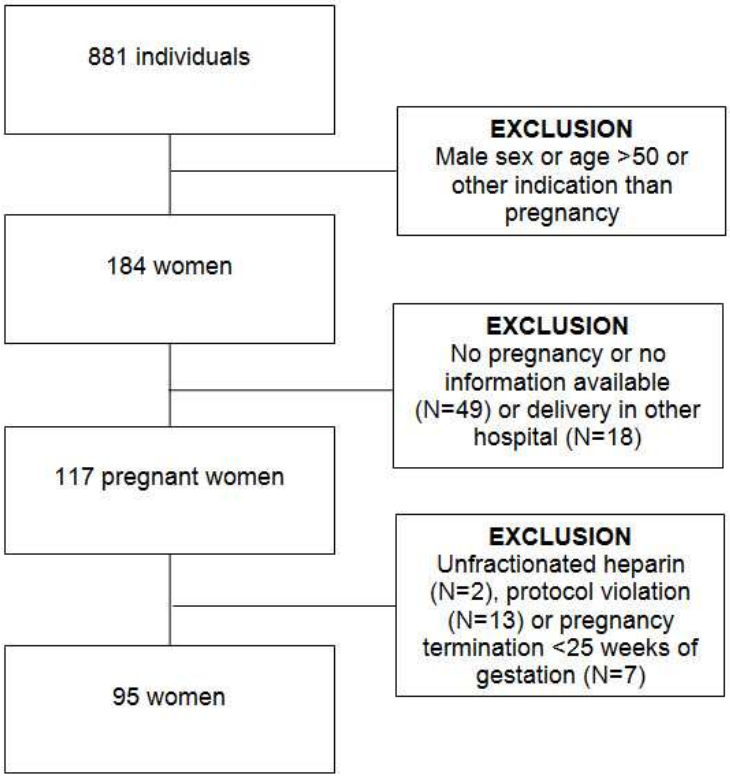
	Item No	Recommendation	Page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	11
Study size	10	Explain how the study size was arrived at	13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13
		(b) Give reasons for non-participation at each stage	6-13
		(c) Consider use of a flow diagram	13
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	15
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	16
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	8-9-16

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9
Discussion			
Key results	18	Summarise key results with reference to study objectives	16
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Figure 1. Inclusion flowchart of women treated with LMWH



61x56mm (300 x 300 DPI)

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

Sara Roshani [a,b], Danny M. Cohn [a], Alexander C. Stehouwer [a], Hans Wolf [c], Joris A. M. van der Post [c], Harry R. Büller [a], Pieter W. Kamphuisen [a], Saskia Middeldorp [a]

Authors' affiliations

[a]Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

[b]Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, The Netherlands

[c]Department of Obstetrics and Gynecology, Academic Medical Center, Amsterdam, The Netherlands

Correspondence: Saskia Middeldorp, Department of Vascular Medicine, Academic Medical Center, F4-276, Meibergdreef 9, 1105 AZ Amsterdam, Phone: +31 (0)20 5665976, Fax: +31 (0)20 6968833, E-mail: s.middeldorp@amc.uva.nl

Keywords: Low-molecular-weight heparin, postpartum hemorrhage, venous thromboembolism

Word count: 2112

Article focus:

- To compare the incidence of postpartum hemorrhage (PPH) (i.e. blood loss> 500 mL in the first 24 hours 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 sever 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 was not associated with 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
- 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

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. We investigated whether therapeutic doses of LMWH increase the incidence of postpartum hemorrhage in a retrospective controlled cohort study.

Methods:

We identified all pregnant women who received therapeutic doses of LMWH between 1995 and 2008 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. We compared the incidence of PPH (blood loss> 500 mL), incidence of severe PPH (blood loss> 1000 mL) and the median blood loss 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). 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:

We observed that therapeutic doses of LMWH in pregnancy was not associated with clinically meaningful increase in the incidence of PPH or severe PPH in women delivered in our hospital although this observation may be confounded by differential

use of strategies to prevent bleeding. A randomized controlled trial is necessary to provide a definite answer about the optimal dose of LMWH in pregnancy.

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 the disadvantage that 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 bleeding, most notably postpartum hemorrhage (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, since 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 uterus, cervix, vagina and perineum. The commonest cause of primary PPH (PPH < 24 hours following delivery) is 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 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 multicenter 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 6/126 (4.8%) and 3/174 (1.7%) of women who were treated with therapeutic doses of LMWH in these 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 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.[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 7 of 8 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.

Material and methods

Identification of study cohorts

By hospital protocol, anti-Xa levels were measured at one-month intervals in women who were treated with therapeutic doses of LMWH or heparinoid during pregnancy. Thus, our study cohort was identified by 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 prior to 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 with 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 administer the last injection the morning prior to the day that induction of labour or a cesarean section was planned. Also women were informed that epidural or spinal anesthesia was contraindicated within 24 hours after the last dose of LMWH. Management of postpartum hemorrhage 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 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 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 to 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 kwn (i.e. type of vaginal delivery [normal versus assisted] or cesarean section [elective versus emergency], perineal laceration degree and ethnicity) to investigate

their interaction with LMWH on the incidence of PPH. Blood transfusion in the first 24 hours of delivery was compared between two groups of the study using the X^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 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 (26-44) weeks in LMWH users and 39 (25-43) in non-users. In both cohorts, almost 93% of vaginal deliveries proceeded spontaneously (normal vaginal delivery) and 7% needed assistance. Almost one-quarter (23 %) of the women treated with LMWH delivered by cesarean sections; half of these were elective, i.e. planned before onset of labour. In the control cohort 10% of the women underwent cesarean sections, most were emergency cesarean sections (90%).

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 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 cesarean section delivery was not statistically significant different between two groups of women.

Median blood loss after vaginal delivery was 250 (range, 50 to 4000) and 300 (20 to 3600) mL in LMWH users and non-users respectively (median difference -50; 95%CI: -102 to 2). After cesarean section, it was 425 (200 to 2000) mL in LMWH users and 400 (100 to 2000) mL 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 (range, 50 to 4000) and 300 (20 to 3600) mL 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 0.6-5.8) 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 localization as the previous PE.

Discussion

We observed that the incidence of severe bleeding during delivery was not increased by using therapeutic doses of LMWH during pregnancy, though 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 as compared to 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 routinely performed, although oxytocics administered in the third stage of delivery have been shown to reduce the amount of blood loss.[20] Therefore we hypothesize 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 since 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 center, 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 cesarian section, the incidence of severe PPH may be more relevant to evaluate since 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 as compared to those who did not, although the certainty of this estimate is limited by the small number of individuals in this stratum. In another study where the doses of the administered LMWH was not specified, the risk of severe PPH for LMWH users (5%) in cesarean sections was surprisingly stated 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 relative risk of PPH in vaginal deliveries. Therefore we compared the median of blood loss between cohorts of LMWH users and non-users considering that median is less sensitive to outliers. The only difference in median blood loss was found in the subgroup of normal vaginal deliveries where 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 use of therapeutic LMWH if similar obstetric measures are taken. Second, we have not measured anti-Xa levels shortly prior to delivery, since this was not part of the hospital protocol. However, the advice given to all women reflects a real life situation (i.e. to discontinue LMWH when contractions started, membranes ruptured or the evening before the planned induction of labour or cesarean 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 any, 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 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 labor start. A randomized controlled trial to assess the safety of therapeutic doses of LMWH to prevent venous thromboembolism in pregnant women is necessary to provide a definite answer about the optimal dose of LMWH in this population.

Acknowledgements

The authors would like to thank Miss Sofie Hamers, medical student, for assisting us with data collection. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors

Competing interests: The authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Addendum

S. Roshani, D.M. Cohn and A.C. Stehouwer collected data. S. Roshani and D.M. Cohn performed the analysis, and contributed equally to this paper. S. Roshani, D.M. Cohn and S. Middeldorp designed the study and wrote the manuscript. A.C. Stehouwer, H. Wolf, J.A. M. van der Post , H.R. Büller , and P.W. Kamphuisen critically reviewed the paper and discussed the analysis. All authors approved the final version.

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 to 200	53 to 116
Dalteparin, IU anti-Xa	9	15000	10000 to 20000	64 to 115
Nadroparin, IU anti-Xa	64			
<75 kg	33	11400	11400 to 15200	48 to 74
≥75 kg	31	15200	11400 to 20900	75 to 117
Danaparoid, IU anti-Xa	3	4000	3000 to 4500	55 to 66
Tinzaparin, IU anti-Xa	3	18000	14000 to 28000	75 to 82

* Doses are presented in mg for enoxaparin and IU for other LMWHs

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)
Cesarean section N (% of all women)	22 (23)	52 (10)
Primary cesarean section, (% of cesarean sections)	11 (50)	5 (10)
Emergency cesarean section, (% of cesarean 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 2 cases was missing, †VTE during current pregnancy

.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
Cesarean 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
Cesarean section	2 (9)	2 (4)	2.5		0.3 to 18.9
Blood loss Median (range)					
Vaginal delivery	250 (50 to 4000)	300 (20 to 3600)	-	-50	-102 to 2
Normal vaginal delivery	200 (50 to 4000)	300 (20 to 3600)	-	-100	-156 to -44
Assisted vaginal delivery	350 (250 to 550)	400 (100 to 2500)	-	-50	-217 to 117
Cesarean section	425 (200 to 2000)	400 (100 to 2000)	-	25	-153 to 203
Primary cesarean section	450 (200 to 1200)	200 (100 to 400)	-	250	-15 to 515
Emergency cesarean section	400 (200 to 2000)	400 (100 to 2000)	-	0	-225 to 225
Blood transfusion N (%)	5 (5)	18 (3)	1.6	-	0. 6 to 4.3

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