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Duration of labor among women with thromboembolic events: A Swedish register study

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ABSTRACT

Introduction: Inflammation is central to initiation of labor and coagulation is closely interlinked with inflammation. Low-molecular-weight-heparin (LMWH) promotes inflammatory cervical remodeling, myometrium contractility and has been associated with shorter duration of labor.
Material and methods: This was a cohort study of 136,661 deliveries 2013–2017, identified in the Swedish Pregnancy Register with prospectively collected pregnancy and labor characteristics. Information of duration of labor was retrieved from the electronic birth records and analyzed with Cox proportional hazard regressions according to previous or current thromboembolic disease (overall) with or without LMWH treatment with non-exposed as reference.
Results: The crude hazard ratio for vaginal delivery was not different between women with thromboembolic disease and women without thromboembolic disease (HR 0.99, 95 % CI 0.91–1.09). A lower hazard ratio for vaginal delivery was observed among women with venous thromboembolism (VTE) with concomitant LMWH use/treatment (adjusted HR 0.86, 95 % CI 0.76−0.98) compared to non-exposed, implying a longer duration of labor in these cases.
Conclusion: Thromboembolic disease was not associated with shorter duration of labor and in presence of LMWH these women experienced longer duration of labor.

Introduction

Inflammation is a central to pregnancy and labor. Across pregnancy, the circulatory inflammatory burden increases and is thought to be important to the maturation process and preparation for active labor [1]. An exaggerated inflammatory response is implicated in adverse pregnancy outcomes including preeclampsia, preterm birth, and in venous thromboembolism (VTE) [1–5]. The pandemic of SARS-CoV-2 has further highlighted the link between hyperinflammation and VTE, resulting in an increased use of anticoagulants during pregnancy and postpartum [6].

Pregnancy is a hypercoagulable state; a physiological adaptation likely occurring to prevent postpartum hemorrhage, which is marked by increased clotting factors and reduced fibrinolysis. However, this adaptation is associated with a more than fivefold increased risk of VTE during pregnancy, and in cases of acquired or inherited thrombophilia, the risk is further amplified [7–9]. Previous associations between thrombophilia and pregnancy outcomes have largely focused on the risk of preeclampsia, intrauterine growth restriction, stillbirth and preterm birth, and to a lesser extent onset and duration of labor. Hemostasis and inflammation are closely interlinked; coagulation triggers an inflammatory response whilst an inflammatory response triggers coagulation with dissemination of fibrin [6,10]. The proinflammatory neuropeptide, bradykinin, which is produced by the fibrinolytic system is able to trigger uterine contractions [11].

Low-molecular-weight heparins (LMWH) are anticoagulants used during pregnancy, either as prophylaxis or treatment for VTE. In addition, despite a lack of evidence [12], LMWH is often used in

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the prevention of placenta-mediated complications [13]. Despite the strong anti-inflammatory properties of LMWH [14], in-vitro studies have demonstrated LMWH to promote the inflammatory process involved in delivery including cervical remodeling, myometrium contractility, which is thought to be associated with increased secretion of interleukin-8 from fibroblasts, and potentially, enhance the effect of oxytocin and prostaglandins [15]. Previous results from studies investigating LMWH and onset of labor and labor duration have been conflicting. Isma et al. found higher rates of preterm birth and lower rates of prolonged labor among 217 women on LMWH treatment during pregnancy, and although not significant, a one-hour shorter duration of first stage of labor compared to controls [16]. Another case-control study found a significant shorter duration of labor (6 *vs*. 9 h) in nulliparous women with spontaneous onset of labor on dalteparin treatment (n = 93) compared to 181 controls [17]. In contrast, a large cohort study accounting for important factors such as body mass index (BMI) and epidural analgesia during labor [18,19]. found no association between LMWH use and diagnosis of labor dystocia [20]. None of these studies examined the role of hemostatic disorders on the associations between LMWH and labor duration. It is plausible that hemostatic disorders, such thromboembolic disease, which is a major indication for LMWH therapy, may confound the association between LMWH therapy and altered duration of labor. Thus, this study aimed to investigate whether thromboembolic disease with and without LMWH therapy influence the duration of labor among nulliparous women in a Swedish population-based setting.

Material and methods

This was a register-based study using data retrieved from the Swedish Pregnancy Register (SPR) including demographic, pregnancy and labor characteristics among 136,661 nulliparous women with spontaneous or induced onset of labor, giving birth to a live born singleton in cephalic presentation from January 2013 until July 2017 among 16 out of 20 counties in Sweden. The SPR is a Swedish national quality register of pregnancy and birth, and has been investigated, validated and presented in detail previously [21,22]. In brief it comprises prospectively self-reported demographic, reproductive and maternal health data collected at antenatal care, as well as information on pregnancy and labor outcomes for the mother and the newborn. It retrieves data from electronic birth records (EBR) and includes diagnoses classified according to International Classification of Diseases 10th revision (ICD-10) [23]. For the present study, parous women, as well as pregnancies with multiple births, stillbirth, breech and pre-labor caesarean section (CS) were excluded, resulting in a study population of 136,661 nulliparous women. Exposure was venous thromboembolism (VTE) overall, defined as a history of VTE before, during pregnancy or within discharge after labor retrieved by diagnostic codes recorded during antenatal visits and/or in-or-outpatient visits at the labor ward according to ICD-10 (Supplemental information 1). Within the SPR, midwives routinely collect information on medication use from the time of registration for antenatal care until delivery. LMWH use during pregnancy was defined as women reporting the use of dalteparin, enoxaparin or tinzaparin from 28 weeks of gestation and onward to capture current use during labor.

Maternal background characteristics included age at delivery (years), height (cm) and body mass index (BMI) calculated from weight at first antenatal visit (kg/m^2). Country of birth was classified into western countries (Europe, North America, Australia and New Zeeland) and non-western countries. Level of education was set to ≤12 and >12 years and smoking at first antenatal visit was dichotomized (yes/no).

Pregnancy characteristics included *in-vitro* fertilization (IVF), pre-gestational and gestational disorders recorded (using predefined check boxes in EBR by the midwife or by ICD-codes in antenatal and labor charts) (Supplement information S1). Gestational length at delivery (weeks) was recorded with preterm birth defined as delivery <37 weeks of gestation. Information on labor onset, recorded in the EBR in a standardized manner by the midwife, was categorized into spontaneous or induced labor. Information on the use of epidural analgesia and oxytocin for induction and augmentation of labor was retrieved from check boxes or ICD-10 codes. Fetal presentation referred to cephalic presenting part at delivery (occiput anterior or posterior), mode of delivery was categorized intro spontaneous vaginal, operative vaginal (forceps or vacuum extraction) or cesarean delivery. Infant weight (grams) and blood loss (ml) within two hours postpartum were recorded.

Main outcome

Duration of labor was defined as start of established contraction until birth, retrieved from the EBR, calculated from patient or midwife reported time (day-hour-minute) of onset of established contractions until the time of delivery (day-hour-minute) registered in 102,507 cases. Time distribution was checked visually, values < the 0.5th and > 99.5th percentile were considered invalid.

Statistical analysis

Characteristics of the population were described according to a diagnosis of VTE with medians with interquartile ranges (IQR) and frequencies. Mann-Whitney U and Pearson's Chi2 test were used to compare between two independent groups. Median time from established contractions to birth was compared with Kruskal Wallis test between the following groups; 1) no VTE and no LMWH (n = 101,693), 2) VTE without LMWH (n = 246), 3) no VTE but LMWH treatment (n = 310) or 4) VTE with LMWH (n = 258) and presented as Box-plots. Associations between maternal and labor characteristics and labor duration were analyzed using simple linear regression expressing change in hours associated with a unit change of the predictor. To evaluate any clustering effect or reporting between counties a mixed model with labor duration under random county factor provided an intra class correlation (ICC) of 2.5 %. Cox proportional hazard regressions was used to analyze duration of labor, where an event was defined as a vaginal delivery (spontaneous or instrumental) and women with intrapartum CS was censored but contributed with time until delivery. The model fulfilled the following assumptions; each woman contributed with only one mode of delivery and the proportional hazard was not time dependent for exposure of VTE (p 0.292) or LMWH (p 0.678). Maternal age, height, country of birth, education, induction of labor, epidural analgesia and gestational length were covariates included in adjusted analysis. Missing values for country of birth and education was included in the analysis. A high grade of multicollinearity was observed visually between infant weight and gestational age (Pearson's correlation 0.59, $p < 0.01$), thus infant weight was not further included in models. In a secondary analysis estimates were stratified on use of epidural analgesia to estimate any interaction effect.

The Regional Ethics Board at Uppsala University approved the study (Dnr 2018/287).

Results

Of 136,661 births, a total of 696 (0.5 %) had a diagnosis of VTE recorded before pregnancy, during pregnancy or within discharge after labor. LMWH therapy, irrespective of indication, at any time

Table 1
Pregnancy and labour characteristics according to a venous thromboembolism (VTE) before, during and after pregnancy compared to no VTE.

	Missing n=	No VTE n = 135,965 (99.5 %)	VTE n = 696 (0.5 %)	*p-value*
Maternal age *(years)*	*35*	28.8 (6.6)	30.8 (7.3)	<0.001
Maternal height *(cm)*	3,872	166 (9)	168 (8)	<0.001
Body mass index (kg/m2)	6,030	23 (5)	24 (6)	<0.001
Country of birth	*14,649*			<0.001
Western [a]		101,255 (83.4)	563 (92.1)	
Non-western [b]		20,146 (16.6)	48 (7.9)	
Education *(years)*	*25,238*			<0.001
≤12		50,232 (45.3)	214 (37.9)	
>12		60,626 (54.7)	351 (62.1)	
Smoking	*14,966*	5,998 (5.0)	32 (5.1)	0.849
In-vitro fertilization	*682*	8,326 (6.2)	69 (9.9)	<0.001
Pre-gestational disorder [c]		2,824 (2.1)	40 (5.7)	<0.001
Gestational hypertension		9,150 (6.7)	58 (8.3)	0.092
Gestational diabetes		1,843 (1.4)	10 (1.4)	0.853
LMWH		437 (0.3)	355 (51.0)	<0.001
Gestational length *(weeks)*		40 (2)	40 (2)	<0.001
Preterm		6,538 (4.8)	48 (6.9)	0.010
Induction of labor		28,098 (20.7)	206 (29.6)	<0.001
Epidural analgesia		68,946 (50.7)	290 (41.7)	<0.001
Oxytocin		72,287 (53.2)	398 (57.2)	0.034
Fetal cephalic presentation				0.518
Occiput anterior		128,892 (94.8)	656 (94.3)	
Occiput posterior		7,073 (5.2)	40 (5.7)	
Mode of delivery				0.001
Spontaneous vaginal		106,530 (78.4)	515 (74.0)	
Operative vaginal		16,035 (11.8)	84 (12.1)	
Cesarean section		13,400 (9.9)	97 (13.9)	
Infant weight (*grams)*	*411*	3,470 (641)	3,402 (613)	0.003
Blood loss *(ml)*	1,096	400 (300)	400 (280)	0.217

LMWH Low-molecular-weight heparin.
Data presented as median (IQR; interquartile range) and n (%). Comparisons between groups by Mann-Whitney U and Pearson's Chi2 test.
[a] Australia, Europe, New Zealand, North America.
[b] Africa, Latin- and South America, Middle east and Asia.
[c] Including hypertension (n = 909), Diabetes (n = 915), Systematic lupus erythematosus (n = 217), Inflammatory bowel disease (n = 1,087).

point of pregnancy was recorded for 1,088 (0.8 %) women and from gestational week 28 and onward for 792 (0.6 %) of women. Women with a history of VTE were on an average older and taller, of western origin and of a higher education level compared to women without VTE. In addition, IVF and pre-gestational disorders were recorded more frequently among these women. A higher proportion of women with VTE delivered preterm, underwent induction of labor, received epidural analgesia and oxytocin during labor and had an operative delivery (Table 1).

Increased maternal age, shorter stature, non-western origin, education >12 years, gestational length, spontaneous onset of labor, epidural analgesia, oxytocin, and increased infant birth weight were factors associated with longer duration from established contractions to birth. LMWH treatment was associated with shorter duration of labor (Table 2).

Median duration (IQR) of labor for women with VTE without LMWH treatment was 9.28 (7.09) hours compared with 8.43 (6.73) hours for women with VTE and LMWH. The corresponding duration for women with no history of VTE was 8.45 (7.15) hours among women without LMWH compared with 7.76 (6.89) hours for LMWH treated (p 0.037) (Fig. 1).

The crude hazard ratio for vaginal delivery for women with VTE overall did not differ from women without VTE (crude HR 0.99, 95 % CI 0.91–1.09) (data not presented in table). Compared with women neither exposed to VTE nor to LMWH, a lower hazard ratio for vaginal delivery was observed among women with VTE receiving LMWH, adjusted for maternal age, height, country of birth, education, induction of labor, epidural analgesia and gestational length (adjusted HR 0.86, 0.76−0.98), implying a longer duration of labor in these cases (Table 3).

By stratifying on epidural analgesia this was only consistent for women without epidural analgesia (Supplemental 2).

Table 2
Relation between maternal and labor characteristics and labor duration analyzed with simple linear regression expressing change in hours associated with a one unit change in the predictor.

	Coefficient	95 % CI	*P-value*
VTE (yes)	0.026	−0.44, 0.49	0.914
LMWH treatment (yes)	−0.52	−0.96, −0.08	0.021
Age (years)	0.01	0.09, 0.10	<0.001
Maternal height (cm)	−0.06	−0.06, −0.05	<0.001
BMI (kg/m^2)	0.00	−0.01, 0.01	0.937
Non-western origin (yes)	0.15	0.057, 0.247	0.002
Education > 12 years (yes)	0.52	0.44, 0.60	<0.001
IVF (yes)	0.12	−0.02, 0.26	0.094
Pre-gestational disorder (yes)	−0.12	−0.36, 0.13	0.353
Gestational length (days)	0.09	0.09, 0.10	<0.001
Induction of labor (yes)	−1.30	−1.38, −1.21	<0.001
Epidural analgesia (yes)	4.05	3.99, 4.11	<0.001
Oxytocin (yes)	4.07	4.01, 4.13	<0.001
Infant weight (gram)	0.003	0.002, 0.003	<0.001

VTE *Venous Thromboembolism,* LMWH *Low-Molecular-Weight-Heparin,* IVF *In vitro fertilization.*

Discussion

The presence of previous or current thromboembolic disease was not associated with shorter duration of labor; in fact, for women with VTE and current use of LMWH increased duration of labor was observed.

To our knowledge this is the first study to investigate the relationship between thromboembolic disease and duration of labor, taking LMWH treatment into account. This was based on a theoretical framework that a persistent or pre-existing pro-inflammatory state following or predisposing for thrombosis would reduce the duration of labor. Infectious-related fibrin

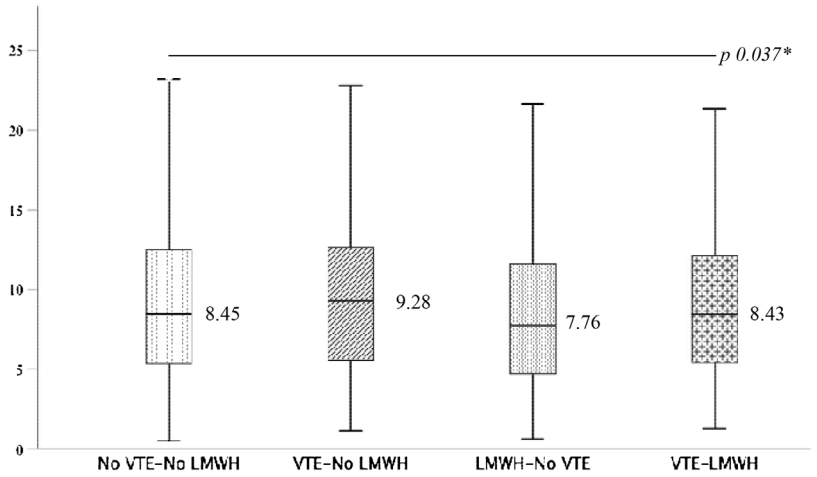

Fig. 1. Median duration of labor (hours) The top and the bottom of the boxes represent the third and the first quartiles. The horizontal line within the box represents the median value. The bars on the side of the box represent the highest and the lowest value.
* Kruskal Wallis test as global between groups.

Table 3
Cox regression with the hazard ratio (HR) of vaginal birth among women with a venous thromboembolic (VTE) event and low-molecular weight-heparin (LMWH) treatment.

Established contractions to birth		
	HR (95 % CI)	Adj HR[a] (95 % CI)
No VTE AND without LMWH (n = 101,511)	1	1
VTE without LMWH (n = 227)	0.96 (0.84–1.09)	0.91 (0.79–1.03)
LMWH without VTE (n = 492)	1.19 (1.06–1.33)	1.11 (0.99–1.25)
VTE with LMWH (n = 277)	1.03 (0.91–1.17)	**0.86 (0.76–0.98)**

Presented as HR (hazard ratio) with 95 % Confidence Interval (CI). Reference: women with no history of VTE and without LMWH treatment.
[a] Adjusted for maternal age, height, education, country of birth, induction of labor, epidural analgesia and gestational length. Included in analysis n = 99,731.

deposition and increased levels of coagulation factors in SARS-CoV-2 infections has further highlighted the link between hyper-inflammation and VTE [6]. Increased levels of interleukins and high-sensitivity C-reactive protein are observed during the acute phase of a thrombosis and at follow up [4,5,9], further supporting this theory. Furthermore, bradykinin, a neuropeptide and product of the plasmin and kallikrein-kinin system can produce uterine contractions [11].

However, our results indicate that a history of VTE before, during or within discharge after labor is not associated with shorter labor. The observed shorter duration of labor with LMWH treatment was inconsistent between groups and was only observed for women with epidural and without VTE diagnosis, whereas women with VTE and LMWH had a lower hazard ratio of vaginal delivery. This is in contrast to two case-control studies reporting one to three hours shorter duration of labor among women exposed to LMWH. Although providing detailed information on labor duration, the case control studies were restricted in size and did not account for important confounders, whereas our study provided information on labor duration as well as pregnancy and labor characteristics in a population-based setting. Supported by in-vitro studies, which identified heparan sulphate proteoglycans in the uterus to be important in cervical remodeling and labor, and these observational trials, a randomized controlled trial was set up to examine the effect of tafoxiparin (a heparin sulfate mimetic) as an adjunct treatment to oxytocin on labor progression (clinical trial number: NCT03001193). Recruitment was completed 2018, and preliminary results indicate lack of efficacy to treat prolonged labor [24]. In line with our results, Sandstrom et al. reported no association between LMWH treatment and reduced risk of prolonged labor in a cohort of 232,104 nulliparous women [20]. That register-based study did not provide details of labor duration, and the outcome was restricted to a diagnosis of primary or secondary dystocia. However, the study by Sandstrom et al. and our study demonstrate the importance of existing register-based cohorts in offering valuable insights into the role of therapeutics prior to the completion of often costly randomized clinical trials. This is important to consider both from a scientific and an ethical perspective. Clinical observations are important and could provide hypotheses, but small trials are often restricted in numbers, prone to selection bias and associations confounded by indication. A randomized trial provides the highest degree of evidence, but could underestimate rare but important risks of interventions and long-term health effects. In addition, their inclusion criteria are often strict and results might be hard to extrapolate to the general population. Further it is time consuming, costly and involves human subjects. Cohort studies with prospectively collected data provide an excellent opportunity to investigate risks and benefits of certain therapeutics.

Despite the population-based setting with a large sample size and detailed information on pregnancy, labor characteristics and duration of labor, we acknowledge there are limitations with the study design and register-based information. LMWH treatment was based on patient and midwife reports at antenatal care with no reliable information of prescribed doses. However, in the study by Sandstrom et al. in an equal Swedish setting, 0.9 % of

nulliparous women had LMWH treatment during pregnancy based on prescription register data, which is in line with our reported rate of 0.8 %. However, only 51 % of women in our VTE group had concomitant LMWH treatment recorded in the last trimester, which indicates an underestimation. It can partly be explained by the fact that the included diagnosis of thromboembolism also comprised superficial thrombosis and a small proportion of VTEs diagnosed postpartum. A misclassification of diagnosis of VTE and LMWH treatment could result in underestimation of association with labor duration as estimates are diluted. No information of cervical dilatation at different time points of labor was available and estimation of labor duration was based on self-reported onset of established contractions. Gross et al., found that patient reported onset of labor accords with midwife assessment of labor onset in less than one third of cases [25]. To evaluate any clustering effect on reporting labor onset between county units, ICC was calculated to 2.5 %, indicating a low risk of heterogeneity and information bias between units. The observational study design limits clear causal interpretations and effects, as treatment is confounded by indication and groups are unbalanced at baseline. In this cohort, women with VTE had higher rates of intrapartum CS. Women with caesarean delivery were censored in the Cox regression analysis, but contributed with time, to account for this confounding factor and estimate the hazard ratio of a successful vaginal delivery. Although, clinical important confounders were included in the adjusted analysis, unmeasured confounders and limited data from registers could bias the results.

Conclusion

The presence of previous or current thromboembolic disease was not associated with shorter duration of labor overall, and there were conflicting results of labor duration of LMWH treatment among different groups.

Author contributions

Susanne Hesselman, Anna-Karin Wikström and Lina Bergman conceived the study. Susanne Hesselman, Anna Wikman and Anna-Karin Wikström managed the data set. Susanne Hesselman conducted the analysis with intellectual input and technical support of Anna Sandström and wrote the first draft. All authors provided intellectual input and contributed to the final manuscript.

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Details of ethics approval

The Regional Ethical Board at Uppsala approved the study the 15th of August 2018 (Dnr 2018/287).

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eurox.2021.100130.

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