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Full Length Article

Prolonged low-molecular-weight heparin use during pregnancy and subsequent bone mineral density☆

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ABSTRACT

Introduction: In contrast to unfractionated heparin (UFH), use of low-molecular weight heparin (LMWH) during pregnancy has not been reported to be associated with a significant decrease in bone mineral density (BMD). The aim of this study was to investigate whether long-term use of LMWH during pregnancy is associated with subsequent decrease in BMD or with increased number of osteoporotic fractures.
Materials and methods: In this observational cohort study BMD was measured by dual energy X-ray absorptiometry (DEXA) 4–7 years after the last delivery in 152 women. Ninety-two women had prolonged LMWH-exposure during pregnancy – 75 as prophylaxis and 17 as treatment for venous thromboembolic event (VTE). Dalteparin and enoxaparin were the LMWH-preparations used. Sixty women without LMWH-exposure served as controls. A questionnaire about lifestyle factors and medical history was filled out by the subjects.
Results: Lumbar spine BMD in the LMWH users was lower than that in the controls both in the prophylactic group (1.22 g/cm^2 vs. 1.27 g/cm^2; $p = 0.03$), and in the treatment group (1.20 g/cm^2 vs. 1.27 g/cm^2; $p = 0.07$). BMD in femoral neck did not differ between the LMWH-users and controls. However, after adjusting for potential confounding factors, LMWH-exposure did not remain associated with decreased BMD in lumbar spine. Use of contraceptive pills was positively associated with BMD in lumbar spine. Incidence of osteopenia was 13% in the LMWH-group and 8% in the control-group, ($p = 0.4$). No osteoporosis or osteoporotic fractures were found.
Conclusions: Prolonged use of LMWH during pregnancy was not associated with subsequent decrease in BMD, osteopenia, osteoporosis, or osteoporotic fractures.

1. Introduction

Since 1980s LMWH has replaced UFH in prevention and treatment of VTE during pregnancy and prevention of recurrent pregnancy loss in women with antiphospholipid antibodies. [1–4] It is still unclear to which extend prolonged use of LMWH is associated with adverse effects earlier reported for UFH, such as heparin-induced thrombocytopenia (HIT), bleeding and heparin-induced osteoporosis (HIO) [4–10]. Pregnancy besides cancer is one of the few situations, where prolonged heparin use is recommended if indicated [11].

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural alterations associated with increased bone fragility and consequent increase in risk of fractures [12]. BMD is expressed either as an absolute value (g/cm^2) or as a T- or Z-score. T-score measures the difference, by number of standard deviations, of an individual BMD from the mean of young female reference population [12]. Osteoporosis is diagnosed when T-score is −2.5 or less, and osteopenia (decreased bone density), when T-score is between −2.5 and −1 [12]. Z-score, in turn, is the number of standard deviations by which a patient's BMD differs from the average BMD of the same age, sex and ethnicity [12].

Bone loss associated with UFH is due to decreased bone formation and increased bone resorption [13] and could explain 2–9% experience of symptomatic fracture after prolonged UFH-use during pregnancy [6, 14]. LMWH might cause less osteoporotic effect by acting only on bone formation [15].

The number of pregnant women using LMWH is growing and the risks of long-term LMWH-use are important to investigate. Pregnant women are mainly young, thus other risk factors for osteoporosis are rare in this population, but prolonged use of LMWH could lead to lower bone mass, becoming relevant when these women were going to enter postmenopausal phase [12].

Our aim was to study whether there is subsequent decrease of BMD in lumbar spine and/or femoral neck after a long-term use of LMWH during pregnancy.

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2. Material and methods

This observational cohort study was undertaken at the Department of Obstetrics and Gynecology, Helsinki University Central Hospital, Finland. The study group (LMWH-group) included 92 women, who received LMWH-prophylaxis or -treatment during their pregnancy. Fifteen women in the LMWH-group had a history of two LMWH-exposed pregnancies. Sixty women without LMWH-exposure served as controls. Participants were invited to the study by a recruitment letter, which included information about the marginal radiation associated with DEXA analysis. A total of 190 recruitment letters were sent to the LMWH-exposed patients and 380 to potential controls. Our primary aim was to select two controls for every case, matched for age and parity. Unfortunately many potential controls declined from DEXA, and thus we succeeded to recruit just 60 controls. Subjects were identified in the electronic hospital database by using International Classification of Diseases-10 (ICD10) codes I73, I74, I80, I81, I82, I83, D68 and M32. The consecutive parity-matched next parturient after the index case without LMWH-exposure was selected as a control. All subjects were Caucasians. Approval was obtained from the local ethics committee.

BMD in lumbar spine and femoral neck was measured with DEXA (Lunar Prodigy advance Full Size, encore software Version 15. GE Medical Systems-Lunar Madison. WI USA). The DEXA was carried out 4 years (median) after the last delivery in LMWH-group and 7 years (median) after the last delivery in control-group. The women were asked to fill out a questionnaire regarding their lifestyle factors (smoking, physical exercise, dietary calcium intake and alcohol use) and medical history, such as, menstrual cycle, underlying diseases, medications, duration of breastfeeding and contraception. The baseline characteristics (age, BMI, gravidity, parity, obstetric history and medical history including regular medication) as well as the data on the type of LMWH, dosing details, time of initiation and duration of the use were retrieved from the electronic hospital database. The calculated total LMWH-dose included all dosages received in all pregnancies together.

The women in the LMWH-group received either dalteparin or enoxaparin. We did not collect the individual exact indications of LMWH-use, other than above mentioned ICD10-codes used to identify LMWH-exposed women, because those were estimated to be irrelevant in terms of the risk of osteoporosis. Normal prophylactic LMWH-doses were standardized: enoxaparin 40 mg/day or dalteparin 5000 IU/day. Weight-adjusted treatment doses were defined as full-treatment doses of LMWH (dalteparin 200 IU/kg/day or enoxaparin 1 mg/kg twice daily). Intermediate doses were 50% of weight-adjusted treatment doses, i.e. enoxaparin 1 mg/kg/day or dalteparin 100 IU/kg/day. The total LMWH-dose during all pregnancies was also calculated.

We approximated the daily calcium intake based on declared calcium-containing food consumption by using Fineli® nutrient composition database [16]. Long-term (>6 months) oral glucocorticoids [17] and antiepileptics [18] were determined as significant medications in terms of osteoporosis risk. Diseases which affect calcium metabolism, for example, primary hyperparathyroidism, Cushing disease, chronic liver, kidney and gastrointestinal (for example celiac disease) diseases and rheumatoid arthritis type diseases were determined as significant diseases in terms of osteoporosis risk [19,20].

The principal outcome variable was BMD in lumbar spine and femoral neck, T-scores and Z-scores were also calculated. Secondary outcome variables included established osteoporosis (T-score < -2.5) and osteopenia ($-1.0 <$ T-score > -2.5) and clinically evident osteoporotic fractures. The null hypothesis was, that there is no difference in BMD between LMWH- and control groups at p-level <0.05. In LMWH-exposed women DEXA-measurement was performed between years 2008 and 2009. Due to delayed funding, DEXA in the control women was carried out between years 2011 and 2012, causing an age difference between LMWH-exposed woman and controls at time of DEXA-analysis. All DEXA-measurements were made by single equipment. The quality assurance of our equipment was performed by daily calibrations and weekly accuracy measurements. During the years 2008–2012 daily calibrations were carried out by using a standard calibration block which includes 3 cavities that simulate the BMD-values 0.5, 1.0 and 1.5 g/cm^2. The BMD of every cavity must be within 0.03 g/cm^2 of the expected value. Repeatability accuracy over the long term was adjusted through weekly measurements by using a skeleton phantom (Accuracy Phantom, SN 21979, BMD 1.265 g/cm^2). The day to day variation of our equipment is 0.01 g/cm^2 and the coefficient of variation is 1.0% (%CV = standard deviation/a percentage of average-BMD) for lumbar spine and femoral neck.

Statistical Package for the Social Sciences Versions 21 and 23 (SPSS Inc., Chicago, IL, USA) were used for analyses. Continuous variables were tested by Student's *t*-test, when normally distributed, else by Mann-Whitney *U* test. Frequencies were compared by Chi-squared test. Dose-effect was calculated by using linear regression. Multivariate regression analysis was used to adjust outcome variables for potential confounding factors. Women with missing values in one or more variables were excluded from the multivariate regression analysis. All tests were two-tailed and p-values <0.05 were considered as statistically significant. In order to achieve 80% power, number needed for both arms was originally calculated to be 80 to detect a 10% difference in BMD between the study groups.

3. Results

The demographics of the study participants are shown in Table 1. Three women did not answer to the questionnaire. One woman did not report her daily calcium-containing food consumption and one woman did not report the amount of her physical exercise per week. Five women did not remember their menarche age and four their duration of lactation, additionally 30 women forgot their menstruation onset time after childbirth. Otherwise questionnaires were complete.

Ten women (10.9%) had weight-adjusted treatment doses and seven women (7.6%) had intermediate doses, the rest 75 women (81.5%) had prophylactic doses of LMWH. The percentage of the

Table 1
Demographics of the study participants.

	LMWH-group	Control-group	p-Value
	n = 92	n = 60	
Age (years); mean (SD)	38.4 (4.9)	43.4 (4.3)	<0.001
BMI (kg/m^2); mean (SD)	24.0 (4.7)	25.7 (4.8)	0.03
Years after the last delivery; median (range)	3.7 (1−11)	6.8 (4–12)	<0.001
Primiparous (%)	29.3	33.3	0.72
Total duration of LMWH (days)[a]; mean (SD)	247 (84)	0	..
Total LMWH-dose; median (range)			
Dalteparin (IU ∗ 10^3), n = 39	1260 (158–3028)	0	..
Enoxaparin (mg ∗ 10^3), n = 53	9.8 (2.5–35.1)	0	..
Ever smoked (%)	41.6	35.0	0.5
Alcohol doses per week; median (range)	2.0 (0–24)	2.5 (0–17)	0.9
Dietary calcium intake (mg); mean (SD)	740 (351)	670 (331)	0.3
Physical exercise (hours/week); mean (SD)	2.3 (1.2)	2.0 (1.5)	0.3
Chronic diseases[b] (%)	4.5	5.0	0.9
Menarche (years), mean (SD)	12.7 (1.4)	12.7 (1.4)	0.8
Duration of lactation (months per each birth); median (range)	7.5 (0–24)	8.5 (0−32)	0.6
Onset of menstruation after childbirth (months); median (range)	5 (1–14)	4 (1–18)	0.9
Oral contraception pill use (years); median (range)	7 (0–24)	10 (0–26)	0.02
Previous bone fracture (%)	32.6	28.3	0.6

[a] All LMWH-exposed pregnancies together (antepartum and postpartum use).
[b] Four rheumatoid type diseases (LMWH-group). One lymphocytic hypophysitis, one ulcerative colitis and one celiac disease (control-group).