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# Indication-based use of low molecular weight heparin during pregnancy: A retrospective study in Northern Greece

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## Abstract

**Introduction:** Venous thromboembolism (VTE) is a condition with high morbidity and mortality rates and presents as the third leading cause of cardiovascular deaths, globally. During the antenatal period, the risk of VTE occurrence increases, therefore, in pregnant women at high-risk for VTE, the use of low molecular weight heparin (LMWH) is recommended. This study aimed to investigate the indication-based administration of LMWH in pregnancy.

**Material and methods:** This was a retrospective cohort study (2019-2022) conducted at the Third Department of Obstetrics and Gynecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece. All pregnant women at the first trimester of pregnancy were eligible. Their physical characteristics were recorded and information about their personal, familial, gynecological and obstetrical medical history was collected. By utilizing the above characteristics, a score of the risk of developing VTE during pregnancy was calculated for each woman, using the algorithm recommended by the Royal College of Obstetricians & Gynecologists.

**Results:** In total, 2,716 pregnant women were included in the study. Of these, 149 (5.5%) received LMWH throughout their pregnancy with only 2 of them (0.1%) having appropriate indications. Of the women not prescribed LMWH, 2,567 (94.5%), none had an indication for LMWH administration. Notably, 495 (19.3%) women had a history of at least one miscarriage and 89 (59.7%) of them used LMWH, regardless of whether they had an indication or not.

**Conclusion:** There was a high percentage of women with no indication for LMWH who, in fact, received this medication. Physicians should refrain their use following evaluation based on appropriate risk factors.

**Key words:** heparin, targeted administration, adherence, screening, Greek

## Introduction

The risk of venous thromboembolism (VTE) increases by 5-10% during pregnancy and by 15-35% during the puerperium<sup>1-3</sup>. The incidence of VTE is significantly higher during the third trimester of pregnancy and the first weeks of puerperium, while pulmonary embolism (PE) is more common during the puerperium and then decreases at 6-8 weeks after labor<sup>4,5</sup>. This condition is a major cause of maternal mortality causing approximately 1.1-1.5 maternal deaths every 100,000 births in Europe and North America<sup>6</sup>.

Low molecular weight heparin (LMWH) is used as a preventative method against VTE, not only for pregnant individuals but also for the general population. Additionally, both unfractionated heparin and low LMWH are safe for the prevention and treatment of VTE antenatally, due to the fact that they do not cross the placenta and thus do not affect the fetus<sup>7,8</sup>. Moreover, the use of LMWH to prevent VTE is recommended by several medical societies due to the fact that it causes fewer cases of hemorrhage with the same antithrombotic efficacy as with standard heparin<sup>4,9-14</sup>.

The administration of LMWH in pregnancy and the puerperium may be based on an algorithm that calculates the risk for VTE and includes three types of factors: pre-existing i.e. high body mass index (BMI), obstetrical i.e. use of assisted reproduction techniques (ART) and transient i.e. hyperemesis gravidarum<sup>15</sup>

The increased rates of maternal morbidity due to venous thromboembolic incidents raises the need to assess the population where LMWH is indicated, the rate of compliance, the cases missed and the risk imposed, overall. Therefore, this study aimed to investigate the targeted or non-targeted administration of LMWH during pregnancy.

## Material and methods

This was a retrospective cohort study including

data from the medical records of the Third Department of Obstetrics and Gynecology, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Greece, from 08/03/2019 to 03/17/2022. The inclusion criteria were pregnant women that attended their first appointment in the first trimester. Information about their personal, familial, gynecological, and obstetrical medical history was collected and somatometric measurements were taken.

More specifically, the following data were collected: age, BMI, smoking, comorbidities (systemic lupus erythematosus - SLE, cancer, cardiovascular disease, nephrotic syndrome, type 1 diabetes in conjunction with nephropathy, sickle cell anemia, intravenous use of toxic substances), varicose veins of lower extremities, a history of VTE related or not to major surgery, an already known high-risk thrombophilia or low-risk thrombophilia and the existence of a family history of VTE. Finally, with regards to the gynecological and obstetrical medical history, data was collected on the number of previous deliveries, history of miscarriages, method of conception, hyperemesis gravidarum in the current pregnancy, immobilization, any surgery antenatally or ovarian hyperstimulation syndrome during the first trimester.

In all cases, the algorithm for the evaluation of risk factors for VTE during pregnancy, labor, and puerperium recommended by the Royal College of Obstetricians & Gynecologists (RCOG) was used<sup>14</sup>. According to this algorithm, the prescription of LMWH is recommended to all women with a total score higher or equal to 4 (Risk score  $\geq 4$ ) for the entire pregnancy and to women with a score of equal or higher to 3 (Risk score  $\geq 3$ ) after 28 gestational weeks.

All women had given their informed consent that their anonymized data could be used for future research. As per standard policy for audit or observational database studies not involving any intervention or modification of the management of the participants, no institutional review was required and obtained<sup>16</sup>.

Table 1: Risk factors and LMWH administration

0		1		2		3		4	
N	%	N	%	N	%	N	%	N	%
27	18.2	47	31.5	47	31.5	26	17.4	2	1.4

The Chi-square test was used for categorical variables. Statistical significance was set at 5%. The SPSS v25 was used.

## Results

### Demographics / History

In total, 2,716 women attending at the first trimester of pregnancy were included in the study. The median BMI was 24.2 kg/m<sup>2</sup> (range 14.9 - 48.9 kg/m<sup>2</sup>), the median age was 32.2 years (range 18-53) and 816 (30.03%) aged >35 years. 1,076 (62.8%) were nulliparous, 584 (21.5%) had a history of miscarriage, 301 (11.1%) were current smokers, 171 (6.3%) conceived via ART, 12 (0.44%) women had co-existing conditions (i.e. cardiovascular or pregestational diabetes mellitus), 6 (0.22%) had SLE, 40 (1.47%) presented with a low-risk type of thrombophilia and 8 (0.29%) had antiphospholipid syndrome. Finally, there was no case with varicose veins of lower extremities, VTE related or not to a major surgery or with a family history of VTE.

### LMWH administration

From the total population of 2,716 women, LMWH was administered in 149 (5.5%) women. Of these 149 women receiving LMWH, only 2 (0.1%) had a risk-score of at least 4, whereas the other 147 (5.4%) did not fulfil the criteria ( $p < 0.001$ ). More specifically, 27 (18.2%) women had 0 risk factors, 47 (31.5%) had 1 risk factor; 47 (31.5%) had 2 risk factors, 26 (17.4%) had 3 risk factors and only 2 (1.4%) had 4 risk factors (Table 1). On the other hand, none of the 2,567 (94.5%) not taking LMWH had a risk-score of >4 risk factors.

Table 2: LMWH administration and previous history of miscarriage

		At least one miscarriage			
		No		Yes	
		N	%	N	%
LMWH administration	No	2,072	80.7%	495	19.3%
	Yes	60	40.3%	89	59.7%

Notably, the percentage of women who had a previous history of at least one miscarriage and were administered LMWH regardless of whether it was medically indicated or not, was 59.7% (Table 2).

## Discussion

We examined the criteria for LMWH administration during pregnancy from RCOG and found that i) about one out of 20 pregnant women take LMWH, ii) in more than 99% of cases receiving LMWH their use was not justified when using the risk calculation algorithm and iii) no cases of failure to prescribe LMWH in high-risk women were found.

During pregnancy, various physiological, anatomical, and metabolic changes take place, which contribute to the development of a transient “acquired thrombophilia”; this in turn leads to an increased risk of developing VTE [1]. This motivated many obstetric societies in the world to create a reliable system of evaluation of the risk factors, with the aim to prevent VTE by the appropriate use of LMWH<sup>4,10-14</sup>.

Based on our findings, the proportion of women taking LMWH for the entire duration of pregnancy is high in our population. Moreover, of the total women with LMWH intake, the vast majority did not meet the criteria for a prescription. In fact, most of them had none, one or two risk factors and they are considered as low-risk for VTE.

Regarding the risk factors, the administration of LMWH to women with at least one previous miscarriage is of particular interest, according to our findings. More specifically, published data have shown that

the antenatal use of LMWH does not increase birth or conception in women with unexplained miscarriages<sup>17,18</sup>. Another point of interest is the fact that even in cases of thrombophilia, women did not benefit from using LMWH<sup>19</sup>. It is widely known that a common cause of recurrent miscarriage is antiphospholipid syndrome; in pregnant women with antiphospholipid syndrome, low dose aspirin (75 - 100 mg/day) should be prescribed before conception, in conjunction with a prophylactic dose of LMWH since the day of conception<sup>20,21</sup>. What is interesting in this study is the high percentage of women in which LMWH was administered. According to a previous study, the indication-based administration of aspirin during pregnancy differed according to the guideline followed<sup>22</sup>.

Of note, there were no cases with risk factors that justified the use of LMWH and had not been prescribed this medication.

In conclusion, all cases where the administration of LMWH was considered of utmost necessity, it was successfully used and as for those who were actually administered LMWH, the majority did not essentially need to use it. Therefore, as far as the prescription of LMWH is concerned, the attending doctor should evaluate the risk factors of every woman in each antenatal appointment.

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