Enoxaparin in Pregnancy: The Clinical Profile of Patients from a High-Risk Ambulatory of West Paraná State

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I. Introduction

The pathophysiology of thrombus formation was explained by Virchow and are constituents of a triad: venous stasis, hypercoagulability and endothelial injury. During pregnancy, all components of this triad are present, with venous stasis caused by compression of the inferior vena cava by the pregnant uterus, the state of hypercoagulation caused by the presence of procoagulant factors in the bloodstream and endothelial damage caused by some gestational phases, such as nesting and childbirth, leading, therefore, that the risk of venous thromboembolism (VTE) is 20 times higher in a pregnant woman than in a non-pregnant woman.1,2

Patients with the thrombophilia diagnosis will present a defect in the state of coagulation, the increase of the hypercoaguability gestational found in pregnant women thrombophobics will lead the training of thrombi to obstetric complications because of the thrombotic effect in the middle of the placental vascularization. In addition, among the risk factors for the occurrence of VTE during pregnancy, the presence of thrombophilia in pregnant women stands out as the main related factor, followed by the previous occurrence of thromboembolic events.3

In turn, the action of enoxaparin is based on preventing the formation and extension of thrombi, acting as a cofactor for antithrombin III, accelerating the inhibition of pro-thrombotic factors, such as IIa and Xa, by up to a thousand times.4,5

In non-pregnant patients, the half-life of enoxaparin is around 7 hours. However, due to the accelerated glomerular filtration rate, the half-life drops to about 4 hours. Thus, in pregnant women there is a recommendation for two daily applications subcutaneously.6

In pregnant patients who are using enoxaparin, it should be suspended 24 hours before delivery and restarted 8 to 12 hours after delivery, in order to avoid spinal hematoma, due to epidural anesthesia and spinal anesthesia. In the absence of sufficient time for such suspension, the heparin antidote should be used: protamine, at a dose of 1mg for each 1mg of enoxaparin received in its last application. Other non-pharmacological measures, such as the use of elastic stockings to prevent DVT, must be maintained during labor.7

Thus, the study of the motivations for the use of enoxaparin, in addition to the analysis of the complications that occurred in high-risk pregnancies during the use of this drug, are necessary so that a considerable number of pregnant women are benefited with the best management of such medication. This will be possible by understanding the indications, contraindications, beneficial effects and possible side effects. The objective of this work is to outline the profile of pregnant women using enoxaparin and to collect data on the diagnoses and thrombophilia underway in these pregnant women.

II. Methodology

This study is characterized by being observational, longitudinal and retrospective, based on the analysis of reports and medical records, looking for
data that related the profile of the pregnant women, the reasons that led them to use enoxaparin and information on the termination of pregnancy. The number of members of the research was 38 patients and the inclusion criterion for being a participant in the study was being pregnant and using enoxaparin.

This study was approved by the Ethics and Research Committee of Centro Universitário Assis Gurgacz (FAG), under registration CAAE nº 91116918.2.0000.5219.

III. Results

The most prevalent age group among the studied pregnant women was those aged between 31 and 35 years old, with 14 representatives (36.8%), followed by the 12 pregnant women aged between 26 and 30 years (31.5%). Patients aged between 36 and 40 years were 6 (15.7%), between 21 and 25 years of age were 4 (10.5%) and the age group with the fewest representatives was pregnant women between 41 and 45 years, with 2 pregnant women (5.3%). The white race was the predominant one, with 34 (89.4%) pregnant women in such a group, in addition to 2 black patients and 2 others with no defined race.

The origin of the service was, for the most part, the private network, with 26 pregnant women in such a group (68.4%). The referral from the private network is justified by the fact that all pregnant women in this group request the protocol to withdraw enoxaparin free of charge through the public system.

In addition, 11 pregnant women (29%) came from their primary health care unit, without interference from the private system. Only 1 pregnant woman (2.6%) was referred from the tertiary hospital for follow-up at the high-risk outpatient clinic. The average waiting time for care, considering the reference from the primary health unit to the first care at the high-risk outpatient clinic, was 10.6 days (± 10 days), with a minimum waiting time of 1 day, and time maximum of 36 days.

The pregnant women had an average gestational age of 10.7 weeks (± 5.7). As for obstetric history, 4 primiparous women (10.5%) were noted, but only 19 of the pregnant women had already had children (50%). This is justified by the high rate of abortions, with 28 of the pregnant women (73.6%) already having at least one previous abortion. On the other hand, 27 of the pregnant women (71%) already had 3 or more previous pregnancies.

The patients, on average, were in the ideal weight range, with an average BMI of 24.6, the highest being 38.7 and the lowest 21.4. Considering the blood pressure within normal limits when the systolic pressure values were between 90 and 140 mmHg and the diastolic pressure values between 60 and 90 mmHg, at the time of the consultation, the presence of 5 hypertensive pregnant women was noted (13.1%) and 5 hypotensive pregnant women (13.1%).

Graph 1 shows the main complaint of pregnant women considered in the study, the most recurrent being that of previous abortions and the need for follow-up during the current pregnancy, with 14 representatives in this group (36.8%). Then, 7 of the pregnant women complained of previous thromboembolic events (18.4%), 4 of the pregnant women were referred for signs and / or symptoms of DVT (10.5%), as well as 4 other pregnant women had no complaints, but would like of the protocol for the enoxaparin gratuity by the public system. Other complaints and / or reasons for referral were: three with lower limb edema, two with vaginal bleeding, two with previous diagnosis of thrombophilia and one due to changes in obstetric ultrasound (delayed intrauterine growth), as shown in Figure 1.

The main group of pathologies that indicated the use of enoxaparin during pregnancy were thrombophilia, with 30 pregnant women with such disorders (78.9%). In addition to these, DVT prophylaxis and / or treatment with enoxaparin was indicated in 8 other pregnant women (21.1%), as shown in Graph 2.

Among the 30 pregnant women with thrombophilia, the mutation of the enzyme Methylene tetrahydrofolate reductase (MTHFR) was the most recurrent, being present in 20 of the patients (66%). The most common mutation was due to the heterozygous mutation of the C677T gene, in 6 patients (20% of thrombophiliacs). In addition to this, there was also a homozygous mutation of the C677T gene and a homozygous mutation of the A1298C gene, respectively, in 4 patients each. The least common MTHFR mutation was the heterozygous of the A1298C gene, recurring in 3 patients (10% of thrombophiliacs). Of the MTHFR mutations, there was an overlap of mutations in the A1298C and C677T gene in 3 patients (15% of the MTHFR), which is illustrated in Table 1.

Other thrombophilia also led to the use of enoxaparin by the pregnant women evaluated. Among these, two pregnant women (6.6% of thrombophiliacs) with G20210A mutation, of the prothrombin gene, were identified, one of whom developed pre-eclampsia during pregnancy. In addition, there was a decrease in protein S in 7 patients (23.3%), 4 of which were associated with other mutations. One (3.3%) of the pregnant women had the Antiphospholipid Antibody Syndrome (APS), due to the decrease in anti-cardiolipin and another 3 pregnant women (10% of thrombophiliacs) had a heterozygous mutation in the Leiden factor V gene.

Of the 30 thrombophiliacs, at least 15 of them (50%) had the wrong prescription of enoxaparin, according to the Brazilian Ministry of Health's High Risk Gestation Manual, since their mutations were heterozygous for the C677T gene or that involved the A1298C gene. No patient with the MTHFR mutation had
a prescription for folic acid and vitamin B6, as recommended in this same manual.

Most pregnancies ended by cesarean delivery, with 32 patients undergoing such interruption (84.3%). There were 2 abortions (5.2%), one at 6 weeks and the other at 8 weeks of gestation. Four of the newborns (NB) were premature (12.5%) and there was the birth of 1 NB small for gestational age (2.7%) and 2 NB large for gestational age (5.5%).

IV. Discussion

Among similar studies, which have analyzed the use of enoxaparin and / or the occurrence of thromboembolic diseases during pregnancy, the age group varied according to the place where it was performed. In Cuba, during the year 2011, MEDISAN et al. They determined that the most prevalent age group was that between 20 and 24 years of age. In turn, in a Brazilian study, it was found that the average age of pregnant women was 29.3 ± 1.1 years, given that it is more in line with what was found in our study, whose average age was 31.3 ± 0.9 years. 8, 9

Gutierrez-Castañeda et al., During a study carried out in 2017, found an incidence of 1.06% of thrombophilics, among 7,727 pregnant women included in the study. However, only 10.9% of such individuals already had a previous diagnosis of thrombophilia, slightly more than double that found in our study, which was 5.2%. 10

Among the obstetric history of such pregnant women, the authors found that only 16% of their population did not experience any abortion episode, since the focus of the study was thrombophilic pregnant women. 10

In comparison to our study, which focused on pregnant women using enoxaparin and / or the occurrence of thrombophilia, the data were provided beforehand, since we presented 36.8% of pregnant women with complaints of previous abortions. Presented as 40 to 50% of acquired thrombophilia present in pregnant women, in studies carried out in the United States of America (USA) and Europe, the Leiden Factor V mutation had no such impact in our study, with only 8% of pregnant women representing such group. 11, 12

In addition to the higher prevalence, the Leiden Factor V mutation also plays an important role in the pregnancy outcome. In a meta-analysis carried out in 2003, this mutation resulted in early and late fetal loss (OR = 2.01; 95% CI 1.13-3.58). 13

In another Brazilian study, also carried out in Campo Grande/MS, it was found that the most common acquired thrombophilia was APS, at the expense of lupus anticoagulant, in 22.6% of pregnant women. In turn, the most prevalent hereditary thrombophilia was protein C and S deficiency, with 41.6% of pregnant women. 14

Several studies involve protein S with recurrent abortions, which may be more common in populations with deficiency of such protein associated with protein C deficiency. In the present study, 7 patients (23.3%) had reduced levels serum protein C, although in 5 of them this finding was associated with other types of thrombophilia.

In contrast to all studies, our data showed that the majority (60%) of the patients were hyperhomocysteinemic, 52% of them at the expense of a homo or heterozygous mutation in the C677T or A1298C genes. Although the casuistry varies between the literature, depending on the design and the population studied, we have been before all of them, since thrombophilia such as APS, protein C and S deficiencies and Factor V Leiden mutation, have had predominance in such works, unlike the MTHFR mutation, which is no more than 3%. 8-11, 13, 14

Regarding the gestational outcome, it was found that our study is in accordance with what the literature proposes, taking into account that the pregnant women were using enoxaparin. The Brazilian prematurity rate is 11.5%, as it is totally in line with the 11% found in our study. 7

Comparing thrombophilics without any treatment, to the same patients after the increase in enoxaparin, a study carried out by Figueiró-Filho et al, in 2012, showed a significant reduction in pregnancy complications. Fetal deaths and abortions, for example, suffered a reduction (OR 0.04; 95% CI 0.02-0.09) and (OR 0.04; 95% CI 0.02-0.09), respectively, in addition to an increase significant increase in the number of live and term births (p <0.005). 14

Compared to a Mexican study with the same population profile, our abortion rate is up. In such a study, the abortion rate was 2.4%, while the sample of our study showed 5% of this occurrence. The way in which childbirth ended was agreed in the studies, with the cesarean rate around 84%. 10

Another justification, which corroborates the good rates and few complications, is the fact that thrombophilia more aggressive to pregnancy, so to speak, are in suppressed numbers. An example of this is the Factor V Leiden and G20210A gene mutations, associated with fetal loss, with OR 2.71 (95% CI 1.32-5.58) and 2.49 (95% CI 1.24-5.00), respectively, 11, 16

Finally, analyzing the indications for the use of enoxaparin during pregnancy, one should analyze the high-risk pregnancy manual, proposed in 2012 by the Brazilian Ministry of Health. The use of prophylactic enoxaparin is indicated in cases where there is deficiency of protein C (activity <72%), protein S deficiency (activity <55%), antithrombin deficiency (activity <85%), heterozygous or homozygous mutation of the Leiden Factor V or G20210A gene and the
Taking into account that the aforementioned manual was in force at the time of data collection, it can be said that there was a mistaken prescription of enoxaparin 50% of thrombophilic pregnant women, in addition to the absence of prescription of folic acid and vitamin B6 in those with mutation of MTHFR.

V. Final Considerations

Pregnant women using enoxaparin had this prescription, in most cases, due to thrombophilia, with the heterozygous mutation of the C677T gene, which codes for MTHFR the most common. The complaint and / or the most common reason for referral to the high-risk outpatient clinic was recurrent abortion and, in general, the pregnant women did not have other risk factors. The mode of delivery in most pregnant women was cesarean section and the complication rates and gestational outcomes were satisfactory.

However, it was noted an exacerbated prescription of enoxaparin, with at least half of thrombophiliacs using the drug without the need, according to guidelines from the Ministry of Health. Due to the cost of enoxaparin, this ends up leading to an exorbitant increase in costs per pregnant woman and, consequently, a deficit in the collective health system.

References Références Referencias

**Figura 1:** Complaint or reason for referral to the high-risk outpatient clinic for pregnant women using enoxaparin. USG: ultrasound; DVT: deep venous thrombosis

**Figura 2:** Diagnoses that led pregnant women in a high-risk outpatient clinic to use enoxaparin during pregnancy. DVT: deep venous thrombosis; MTHFR: Methylene tetrahydrofolate reductase; APS: antiphospholipid antibody syndrome
### Table: Mutations responsible for the change in the MTHFR enzyme in pregnant women using enoxaparin in a high-risk pregnancy clinic

<table>
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<td>30</td>
</tr>
<tr>
<td>C677T – Homozygosis</td>
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<tr>
<td>A1298C – Heterozygoses</td>
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<tr>
<td>A1298C – Homozygoses</td>
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</tr>
<tr>
<td>A1298C + C677T</td>
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**Figura 3:** Mutations responsible for the change in the MTHFR enzyme in pregnant women using enoxaparin in a high-risk pregnancy clinic