The Role of Low Molecular Weight Heparin in Pregnancies of Patients with Inherited Thrombophilia that Have Presented (and) Thrombotic Complications During Previous Pregnancies

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What is presently known is that thromboembolic disease represents a major cause of morbidity and mortality during pregnancy. To this we add a rare but not negligible pathology, acquired and inherited thrombophilia, which increases the predisposition for thrombotic events during pregnancy. In this article, what has been studied is the impact that LMWH has on patients with inherited thrombophilia, both the conventional FV, FII and the newly introduced MTHFR, PAI, FXII, factors which are often combined.81 patients have been taken into consideration / included in study, with the following anterior results, before the patients discovered their illnesses, thus before following treatment: first trimester or advanced pregnancy loss, IUGR, premature birth or secondary placental thrombotic complications such as: preeclampsia, DPPNI or dead fetuses, as well as maternal thrombotic accidents. The administration of LMWH decreased the rate of pregnancy loss compared to untreated pregnancies is statistical significant (p= 0.004), there were fewer DPPNI (p= 0.006), and no intrauterine deaths. We also compared the occurrence of thrombotic events during treated and untreated pregnancies and we observed significant differences in this groups (p= 0.001). There was also a sufficient number of patients with new types of thrombophilia included in the study to demonstrate the impact it has on pregnancy. LMWH improves the situation of women with thrombophilia during pregnancy.

Keywords: Inherited thrombophilia, LMWH, pregnancy complications

Even the pregnancy itself represents a state of acquired hypercoagulability, with an increase in coagulation factors and a decrease in fibrinolysis activity, a state which occurs naturally and which itself predisposes to deep vein thrombosis, especially as the venous return slows down due to the pregnant uterus favoring stasis. To this, thrombophilia [1] must be added as a factor, favoring deep vein thrombosis, thromboembolism [8-13], pulmonary embolism, gestational vascular complications with first and second trimester pregnancy losses, intrauterine fetal deaths, preeclampsia, DPPNI and IUGR.

These adverse effects occur in about 15% of pregnancies and are a major cause of fetal and maternal morbidity and mortality, and 50% of thromboembolic events that occur during pregnancy do so in thrombophilic patients.

Inherited thrombophilia refers to genetic mutations on the following factors: FV, prothrombin FII, G 20210A position, S and C protein deficiency and the most thrombogenic but also extremely rare is the antithrombin III deficiency. The prevalence of thrombophilia inherited in Caucasians is 15% (see ARACIC article) and is found in up to 50% of patients with VTE. Thrombophilia can be combined, associating several factors.

In this article we also included patients with new hereditary thrombophilias, which are still controversial and studies are rare for this reason: polymorphism in plasminogen activator inhibitor (PAI), methylene tetrahydrofolate reductase gene polymorphism, which is why we also have included this kind of patients in the study.

LMWH has been used as a treatment by many clinicians, and many studies have been done on enoxaparin and dalteparin, compared between themselves and with aspirin. It is often used even before the thrombophilia is proven, even if the effectiveness in this case is not constant. The reason is that the LMWH pregnancy was found to be safe [4, 17].

What we have followed in this study is precisely the efficacy of LMWH administration on inherited thrombophilia pregnancies that presented complications to previous pregnancies in the absence of LMWH treatment.

Complications found in previous pregnancies were: pregnancy loss at various gestational age, intrauterine fetal death, premature birth, preeclampsia [14, 16], DPPNI, maternal thromboembolic events.

The study includes patients with conventional FV, FII, possibly low S and C proteins, and PAI and MTHFR mutations from the newly included thrombophilic patients.

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 # Athors with equal contribution

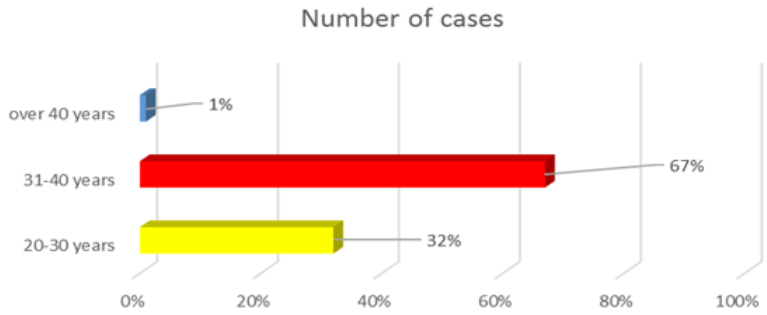

Fig.1. We plotted the number of cases grouped by age

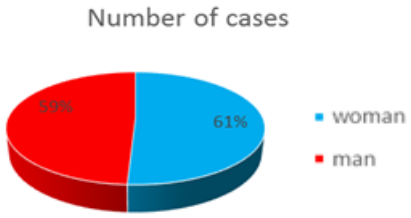

Fig.2. We plotted the number of cases depending on the sex of the fetus

Experimental part

Method

I will include in my study a cohort of 81 inherited thrombophilia patients who have had a history of thrombotic events on previous pregnancies. The studied period was 2010-2017. The patients included were recruited from Brad Municipal Hospital, Deva County Hospital, Hunedoara Municipal Hospital and Dr. Mitranovici's Cabinet.

The inclusion criteria were: patients with a history of thrombophilia without uterine abnormalities, no TORCH infections during pregnancy, diabetes or endocrine abnormalities, no chronic HBP or renal disease, no genetic abnormalities, drug abuse, abnormal fetal screening or karyotype or congenital anomalies.

All patients with sterility and infertility were administrated in preconception LMWH (Nadroparina Calcica) and also when thrombophilia was discovered at the various periods of pregnancy. Patients also received preconceptionally and during pregnancy, folic acid and supplemental vitamins. Thrombotic events from previous pregnancies were also : I trimester pregnancy loss (≤12 weeks), second trimester pregnancy loss (12-21 weeks), IUGR, but according to the criteria adopted for the local population respective to the age of the pregnancy and fetal sex, preeclampsia with BP ≥160 / 110 mm Hg, proteinuria ≥5g / 24h, HELLP Syndrome, preterm delivery in less than 38 weeks, maternal thrombotic events during pregnancy such as: deep vein thrombosis, microembolies, etc.,intrauterine fetal death DTPNI. All patients were treated with LMWH (Nadroparina Calcica). Initiation of the treatment was done in the following pregnancy stage: preconceptionally a case at 10 weeks, one case at 15 weeks and two at 30 weeks. The treatment used was Fraxiparin 0.4 IU / day, only in two cases 0.6 IU / day, in two cases increased from 0.4 to 0.6 IU / day, and in one case received treatment 2x0.6 IU / day.

All of the pregnancies have been correctly supervised with repeated ultrasound examinations, blood pressure monitorization and blood tests including platelet number. The treatment started at the moment of introduction, spanned the entirety of the pregnancy and then six weeks after birth.

The main results were defined as due date pregnancies, abortions in different pregnancy stages, premature births (≤37 weeks). Complications , or secondary results, were defined as : preeclampsia, intrauterine fetal death, DPPNI, IUGR, thromboembolic complications during pregnancy or puerperium.

Types of birth, weight, sex, the Apgar score of the newborn were all taken into consideration. The results of the treatment with LMWH have been compared with previous, untreated pregnancies of the same women .The studied types of thrombophilia have been the conventional ones, with FV, FII G20210A, possibly protein S or C deficiency, but also the new ones : MTHFR, possibly PAI , FXIII.

All our data were processed by using two programs SPSS and Microsoft Excel.

Results and discussions

50 women would have been necesarry for the study to be valid. The number of patients that have been studied is 81. Based on the data obtained after the protocol has been created, among the women who did not receive treatment the percentage of spontaneous abortion (first and second trimester) has been 21% and after treatment with LMWH, 4.9%.

I have only included in the study those patients who got pregnant while under treatment with LMWH, or who were already pregnant and diagnosed with thrombophilia during their pregnancies, which is the reason why sterility among treated patients was 0, compared to the untreated patients, where it was 40, thus a percent 49.4%, and while a value P could not be calculated, the results are conclusive.

Furthermore, amongst the treated patients, there is a statistically significant decrease in the number of DPPNI, with p= 0.006, with the rate of fetal death likewise decreased (p= 0.004).

In order to have a better characterization of our sample we computed same descriptive statistics. The current study includes 81 women, with the average age of 33.6/4.31 years. The most frequent age was 38 years (16.0%), followed by 30 years (12.3%).

We considered some exclusion criteria such as: acute infection including TORCH, gestational diabetes, metabolic disorders, endocrine abnormalities, chronic HTA, renal affections, immunosuppressant drug abuse, abnormal fetal screening, karyotype and congenital abnormalities, uterine abnormalities, placental abnormalities, umbilical cord insertion abnormalities. Centralized table for complications in women antecedents without treatment versus pregnant with treatment. For each category the data from the above tables were extracted and the statistical differences between the percentages were calculated by the square chi test, if the value of p is less than 0.05 we have statistically significant differences. All the data are shown in table1.

The weight values of the fetus (of the born ones) are between (1450; 4050) grams and the average value is 3026.8 g.

At this time, there were 4 thrombotic events, 4.9% versus the time without treatment where there were 18 (22.2%) events, the difference is statistically significant, the p value is less than 0.001. In the same tame another important point is the moment when the tratament is induced. This data are plotted in figure 4 and figure 5.

According to our study, LMWH administration brings improvements in the patient's pregnancies compared to untreated pregnancies. The most obvious improvement

Mutations	Antecedents without treatment		Pregnant with treatment		p value
	number	%	number	%	
Abortions	17	21.0	4	4.9	**0.004**
Premature birth	2	2.5	3	3.7	0.98
DPPNI	11	13.6	1	1.2	**0.006**
Early death	1	1.2	-	-	-
Late death	-	-	-	-	-
PE	2	2.5	4	4.9	0.95
HTA	-	-	9	11.1	-
Fetal death	15	18.5	1	1.2	**0.004**
HELLP	2	2.5	-	-	-
IUGR	1	1.2	6	7.4	0.11
Sterility	40	49.4	-	-	-

Table 1
WE COMPUTED A MAN WHITNEY TEST IN ORDER TO SEE IF THERE ARE ANY SIGNIFICANT DIFFERENCES BETWEEN OUR GROUPS

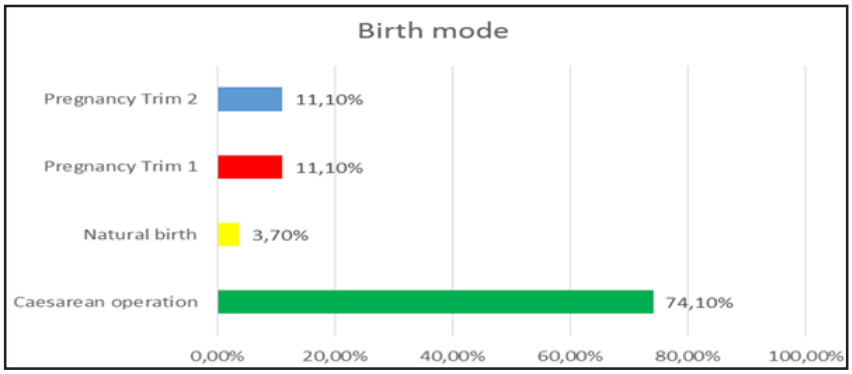

Fig. 3. We plotted the type of birth for our subjects

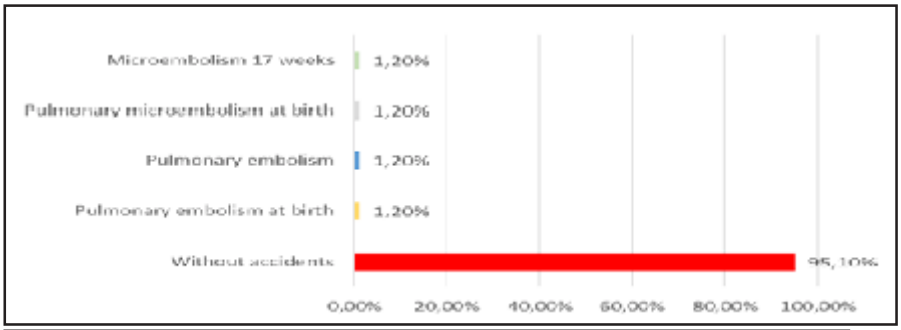

Fig.4. Thrombotic maternal accidents

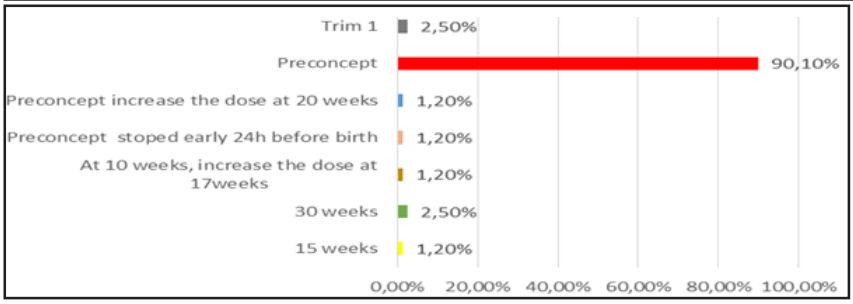

Fig.5. The moment of treatment introduction

has been reported in women with sterility, abortions and DPPNI.

My study shows consistent results with that performed by Aracic on uncontrolled cohorts [2] and two randomized controlled trials [1, 7]. These studies were conducted with LMWH Enoxaparin vs. Aspirin, demonstrating the efficacy of LMWH, but comparing 40 mg Enoxaparin with 80 mg Enoxaparin has not shown any improvement. This was the main reason I opted for a small dose of Fraxiparin (Calcic Nadroparine), another reason being to reduce its adverse effects. Increased dosing has proven efficacy in patients with a history of maternal thrombotic events or the occurrence of thrombotic events on pregnancy under study

Other important results were: reduction of premature births, lack of fetal intrauterine death on the treated pregnancy, decrease of preeclampsia and DPPNI as well as IUGR with an average weight of 3026.8 g.

Referring to other studies, we note a lack of standardization of LMWH administration criteria in the case of Fawzy et al. [5], which found beneficial effects of LMWH administration, not sustained by Ferrazzi's studies [6] and Martinelli [2, 3]. Martinelli's study, however, was widely criticized for lack of specific randomization criteria and insufficient reporting of results. Compared to their studies, in our study all patients presented complications to previous pregnancies for which they did not receive treatment. We can not compare our study with the literature because there is little data that makes a correlation between MTHFR and complications on pregnancy, and the literature results are contradictory. As a SWOT analysis: Our study is strong by the impact of new thrombophilia on pregnancy complications, a little bit analyzed so far, as well as the improvement seen in the management of LMWH in these cases. Additionally, there is a sufficient number of new patients with new thrombophilia included in the study to demonstrate its impact on pregnancy, complications occurring equally with conventional

thrombophilia, the impact being important and thus a working hypothesis for future research appears. Thus, the study shows that thrombophilia screening requires inclusion of MTHFR and PAI in women who had negative outcomes on previous pregnancies.

Like the SWOT analysis, the strength of the study consists of the strict criteria we used to include in the study, the exclusion of women with acquired thrombophilia, the analysis of thrombophilia genes mutations, the separation of thrombosis in conventional and new ones.

The weakness of the study, or its limitation, is the lack of a control group to receive placebo. This was an impediment to recruiting patients, nobody agreeing to taking placebo or receiving treatment after devastating failures in past pregnancies. In fact, it is unethical in a pregnancy clinical study to impose a placebo when we discuss with a pregnant mother with a child.

Another limitation of the study I had in the histopathological analysis of placenta on the patients included in the study.

Conclusions

Our results suggest that the use of LMWH as a treatment for patients with inherited thrombophilia who had complications on past pregnancies reduces pregnancy failure rates, pregnancy loss materialized at various gestational ages, severe complications such as premature birth, fetal death, intrauterine death, IUGR , HELLP, DPPNI, thromboembolic accidents. There were selected precise bias, with generally improved results through a more careful follow-up of LMWH administration. According to the study, it seems opportune to include MTHFR and IAP in the screening of women with severe complications on previous pregnancies. Prior to any final clinical recommendations in both LMWH administration and inclusion of MTHFR and PAI in screening, more studies would be needed on a wide range of participants.

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