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Research Article

Effects of Low-Molecular Heparin on Pregnant Women with Factor V Mutation (GA Genotype)

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Abstract

Objective:

To study the clinical laboratory results of heparin prophylaxis in women with FVL (1691) GA mutation with severe APC resistance.

Material and methods:

A single-center randomized controlled study of 141 pregnant women with FVL mutation (GA genotype) with APC resistance (normalized ratio of 0.49 or less) at 7-8 weeks of gestation has been conducted. The study group consisted of 70 patients who underwent courses of heparin prophylaxis during 14 days from 7-8 weeks of gestation. 71 pregnant women who received no antenatal LMWH prophylaxis were in the control group.

Results:

Prophylactic doses of LMWH decreased thrombin generation from 22 weeks of gestation: Peak thrombin by 9-11% ($p < 0.05$) and ETP by 4-9% ($p < 0.05$), also there was a decrease in APC resistance from 12 weeks by 9-14% ($p < 0.05$) compared to pregnant women receiving standard prophylactic measures. Heparin prophylaxis in women with FVL (1961) GA mutation from 7-8 weeks of gestation reduced the absolute risk (ARR, Absolute Risk Reduction) of placenta-mediated pregnancy complications: PE by 29.5% [ARR: 29.5; $p = 0.0003$; NNT: 3.4, 95% CI (2,35-6,12)], FGR by 23.8% [ARR: 29.5; $p = 0.0016$; NNT: 4.2; 95% CI (2.8-8.7)] and PTL by 12.6% [ARR: 29.5; $p = 0.0242$; NNT: 5.8; 95% CI (3.7-14.1)].

Keywords: APC resistance; Factor V Leiden; Fetal growth restriction; FVL (1691) GA genotype; Heparin prophylaxis; Nadroparin calcium; Preeclampsia; Thrombin generation

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Abbreviations

APC: Activated Protein C
APS: Antiphospholipid Syndrome
AUC: Area Under Roc Curve
CER: Control Event Rate
DBP: Diastolic Blood Pressure
EER: Experimental Event Rate
ETP: Endogenous Thrombin Potential
FGR: Fetal Growth Restriction
FVL: Factor V Leiden
IL-6: Interleukin 6
LMWH: Low Molecular Weight Heparin
NNT: Number Needed To Treat
NR: Normalized Ratio
PCR: Polymerase Chain Reaction
PDONLP: Premature Detachment of a Normally Located Placenta
PE: Preeclampsia
PMC: Placenta-Mediated Complications
PTL: Preterm Labor
RL: Reproductive Loss
ROC: Receiver Operating Characteristic
RRR: Relative Risk Reduction
SBP: Systolic Blood Pressure
TGT: Thrombin Generation Test
TNF-α: Tumor Necrosis Factor-A
U/S: Ultrasound
VTEC: Venous Thromboembolic Complications
ARR: Absolute Risk Reduction
HB-EGF: Heparin-Binding Epidermal Growth Factor

Introduction

To date, Preeclampsia (PE), Fetal Growth Restriction (FGR) and Premature Detachment of a Normally Located Placenta (PDONLP)

remain the main causes of perinatal and maternal morbidity/mortality [1,2]. The ambiguity of reliable data on the etiology and pathogenesis of these placenta-mediated conditions does not allow to develop a universal complex of measures for their effective prevention in the population. One of the proven risk factors for disrupting placenta formation is the genetic thrombophilias, in particular Factor V Leiden mutation [1,3,4]. This is a point mutation of the proaccelerin factor gene, accompanied by the replacement of the guanine nucleotide by adenine at position 1691 (FVLG1691A), which leads to the replacement of the amino acid Arginine (Arg =R) by the amino acid Glutamine (Gln =Q) at position 506 (FV R506Q) in the protein chain, which is the product of this gene. In this case, the polypeptide loses one of the activated protein C cleavage sites which leads to factor Va resistance to Activated Protein C (APC resistance) accompanied by an increase in thrombin generation [5-7]. The resulting imbalance can lead not only to increased coagulation potential [8-14], but also to the disorder of invasion and placentation, which in the future can manifest itself clinically in placenta-mediated complications [2,15-17]. In particular, according to available data, FVL (1691) GA increases the risk of PE by 2.19; FGR by 2.68 and PDONLP by 4.7 [4,18].

In the world practice, the use of Low Molecular Weight Heparins (LMWH) has been repeatedly considered as prevention of PE and FGR in groups at high risk for gestational complications. However, the emphasis was not on the anticoagulant properties of LMWH, but on its additional effects during the development of trophoblast [19-23]. Nevertheless, the results of studies on heparin for gestational complications prophylaxis in women with a history of gestational complications can be considered contradictory [24-32], which, apparently, is caused by different inclusion criteria and insufficient stratification of patients into risk groups, based on individual characteristics, as well as on LMWH administration method.

In a Cochrane review of 1228 women, the researchers concluded that the use of LMWH in women with an unexplained recurrent miscarriage is not justified. According to this document, the effect of LMWH on pregnancy outcomes in patients with recurrent miscarriage with underlying genetic thrombophilia has not been proven and requires further randomized controlled trials [33].

In our prospective cohort study published earlier, which included 500 women with FVL (1691) GA mutation, it was shown that APC resistance ≤0.49 [Normalized Ratio (NR)] can be considered as a prognostic marker for PE (Area Under Roc Curve (AUC)-0,839, p <0.0001) and FGR (Area Under The Roc Curve (AUC)-0.867, p <0.0001) with the greatest accuracy at 7-8 weeks of gestation [34]. We have found no studies investigating the effectiveness of LMWH in preventing placenta-mediated complications considering APC resistance, except for a publication that includes a small sample of 4 pregnant women [35], which was the reason for the present study.

Objective

To study the clinical laboratory results of heparin prophylaxis in women with FVL (1691) GA mutation with severe APC resistance.

Methods

Study population

On the basis of the clinical departments of FSBEI HE ASMU of the Ministry of Health of the Russian Federation, a single-center randomized controlled study of 141 pregnant women with FVL mutation (GA genotype) with APC resistance ≤0.49, determined at 7-8 weeks, was conducted from 2015 to 2017. The design of the study is shown in figure 1.

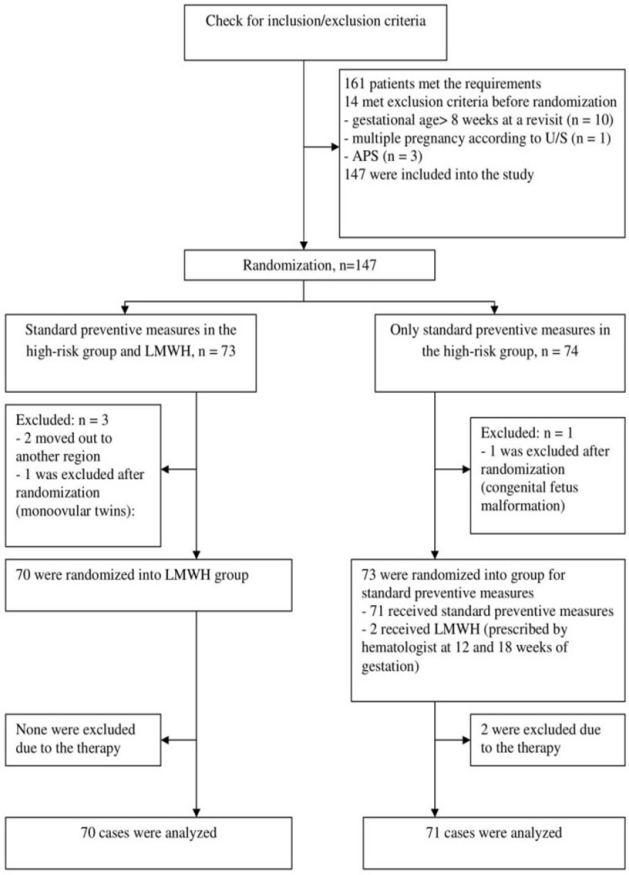

Figure 1: Study profile.

- **Inclusion criteria:** FVL (1691) GA with APC resistance ≤0.49; normal singleton pregnancy, occurring in the natural cycle; gestational age of 7-8 weeks.
- **Exclusion criteria:** FVL (1691) GG/AA genotype; genital organ anomalies; multiple pregnancies; pregnancy, resulting from assisted reproductive technologies; extragenital disease in the stage of decompensation; autoimmune diseases, including antiphospholipid syndrome; chromosomal aberrations in spouses.

The study was approved by the local ethical committee of FSBEI HE ASMU of the Ministry of Health of the Russian Federation (Protocol No. 5 of 25.06.2009).

In total, during the period from 2015 to 2017, 161 patients, who met the inclusion criteria, were selected. All patients had an intermediate risk of Venous Thromboembolic Complications (VTEC) and, according to the recommendations of the world community, did not need antenatal thromboprophylaxis [36,37]. At the stage of group formation, 20 patients left the study (Figure 1): 14 had exclusion criteria before randomization; 4 were excluded in the first trimester of

pregnancy (2 went to another region, 1 had monoovular twins and 1 had fetal malformations), and 3 patients left the control group at the observation stage, because they needed LMWH upon the hematologist's prescription due to DVT episodes. As a result, 141 patients entered the study. The main group consisted of 70 pregnant women (mean age 30.2±4.7) who underwent heparin prophylaxis from 7-8 weeks of gestation. 71 pregnant women were in the control group (mean age 30.3±3.9), where no antenatal LMWH prophylaxis was given. Block randomization was used [38,39].

Blood collection

Venous blood was taken from the ulnar vein into VACUETTE tubes with a 9:1 sodium citrate buffer solution (9 NC Coagulation sodium citrate 3.2%). The blood was centrifuged at 1400 g for 15 min at the room temperature, resulting in platelet poor plasma, where APC resistance was measured for 2 hours. Before the thrombin generation test, the plasma was stored at -40ºC in the interval from 1 day to 1 month in a MDF-192 Ultra low temperature freezer ("Sanyo").

Laboratory assays

All patients underwent dynamic study of APC resistance and thrombin generation (calibrated thrombography by Hemker [40]) at 8 points: 7-8 weeks, 12-13 weeks, 18-19 weeks, 22-23 weeks, 27-28 weeks, 32-33 weeks, 36-37 weeks and 2-3 days after delivery.

APC resistance was measured with the "Factor V-PC-test" (Technology-Standard, Russia), an analog of the corresponding set of reagents produced by Siemens, Germany. To study the thrombin Fluoroskan Ascent "Thermo Fisher Scientific" (Finland) with "Thrombinoscope 3.0.0.26" software was used. Coagulation of the test plasma was performed in the presence of 5.0 pmol of tissue factor and 4 μmol of phospholipids (PPP-Reagent 5 pM, Thrombin Calibrator, FluCa-Kit).

Molecular genetic testing of the gene alleles of Factor V Leiden (F5 Arg 506 Gln) was performed using Real-time PCR with reagents from "Litekh" SPA (Russia). The material for the study was human genomic DNA taken from peripheral blood leukocytes.

Heparin prophylaxis

With APC resistance NR ≤0.49, determined at 7-8 weeks of gestation the patients of the study group were prescribed 0.3 mg of nadroparin calcium (2850 IU anti-Xa) 2 times daily for 14 days. If deemed necessary (with NR ≤0.49) repeat courses of heparin prophylaxis were given-at 18 weeks in 55.7% of cases (39 of 70), at 28 weeks in 54.3% of cases (38 of 70).

Noteworthy is that in both groups, patients at high risk of preeclampsia (52.9% (37 of 70) in the study group and 42.1% (32 of 71) in the control group, p >0.05) received prophylactic doses of acetylsalicylic acid (75 mg per day) according to the clinical protocol [41].

The endpoints determining the efficacy of LMWH were: The number of cases of moderate/severe PE, FGR and PDONLP episodes and the number of induced Preterm Labor (PTL).

Preeclampsia was determined according to International Consensus Criteria: Systolic Blood Pressure (SBP) ≥140 mmHg and/or Diastolic Blood Pressure (DBP) ≥90 mmHg; in women with initial hypotension, an increase in SBP by 30 mmHg and/or DBP by 15 mmHg compared to the initial one (arterial blood pressure in the first trimester of pregnancy), accompanied by proteinuria: A daily protein loss of 0.3 g/l and more, any proteinuria recorded in a single portion of urine [42]. Fetal growth restriction was defined as a condition in which the fetal body weight and/or fetal abdomen circumference is below 10% for a given gestational age and/or the morphological maturity index lags 2 or more weeks from the true gestational age [43]. The induced preterm labor was the delivery at 22^{+0} to 36^{+6} weeks, performed due to mother's critical condition (increasing severity of somatic diseases, pregnancy complications) and/or fetus (progressive decline, antenatal fetal death).

Statistical calculation

Statistical processing of data was carried out using the MedCalc Statistical Software version 17.9.7 (license BU556-P12YT-BBS55-YAH5M-UBE51). The verification of the variation series for the normal distribution was carried out using the Shapiro-Wilk's W-test. Laboratory data are presented as a Median (Me), 95% confidence interval and interquartile range [25^{th} and 75^{th} percentile]. Comparison of the series was performed by nonparametric methods (the Mann-Whitney U test). The main criteria for evaluating the effectiveness of therapy are defined as: Absolute risk in the study group (SAR) and control group (CAR), Relative Risk (RR), Absolute Risk Reduction (ARR) and Relative Risk Reduction (RRR), Number Needed to Treat (NNT) 95% confidence interval (CI-95%) for RR and NNT. The significance level (p) is defined as $p < 0.05$.

Results

At the first stage of the study, the clinical characteristics of patients were studied according to the traditionally considered risk factors for development of placenta-mediated conditions. As a result, it was shown that both groups were representative in age, thrombotic and reproductive history and somatic pathology (Table 1).

Further analysis showed that patients with FVL (1691) GA had elevated values of thrombin generation at 7-8 weeks (ETP median by 1.3: 1999 nmol × min vs 1542 nmol × min, p <0.0001; peak thrombin by 1.5: 423 nmol/l vs 290 nmol/l, p <0.0001) in comparison to the physiological norm, which had been published earlier [44]. As pregnancy developed, these values acquired statistically significant differences depending on whether heparin prophylaxis was performed or not (Figures 2 and 3).

In particular, a decrease in thrombin generation due to LMWH intake was determined from 22 weeks of gestation: Peak thrombin by 9-11% and ETP by 4-9%.

Along with a predictable response of TGT main parameters to the LMWH, the decrease in APC resistance (NR) was unexpected (Table 2).

From the data presented, it can be seen that the APC resistance during LMWH intake decreased statistically significantly from 12 weeks of pregnancy, in contrast to the results in the control group (Figure 4).

In general, due to heparin prophylaxis, a decrease in APC resistance by 9-14% (p <0.05) was found in comparison to pregnant women receiving standard preventive measures.

Somatic and Reproductive History of the Groups	LMWH "+" n=70		LMWH "-" n=71		p
Hypertensive heart disease	20	28.6%	17	23.9%	0.624
Varicose disease of lower extremities	34	48.6%	31	43.7%	0.584
Excess body weight (BMI >25)	29	41.4%	28	39.4%	0.241
Age >35 years old	10	14.3%	16	22.5%	0.091
History of thrombotic complications	20	28.6%	18	25.4%	0.118
History of 3 or more reproductive losses	12	17.1%	9	12.7%	0.742
History of an antenatal loss	7	10.0%	5	7.0%	0.626
History of preeclampsia	17	24.3%	15	21.1%	0.447
History of FGR	15	21.4%	13	18.3%	0.464
Premature detachment of the placenta	3	4.3%	5	7.0%	0.701
Spotting in 1st trimester, requiring hospitalization	12	17.1%	11	15.5%	0.265

Table 1: Somatic and reproductive history of patients with Factor V Leiden [FVL (1691) GA] of the groups.

Abbreviations: LMWH "+"-patients who received heparin prophylaxis; LMWH "-"-patients without heparin prophylaxis.

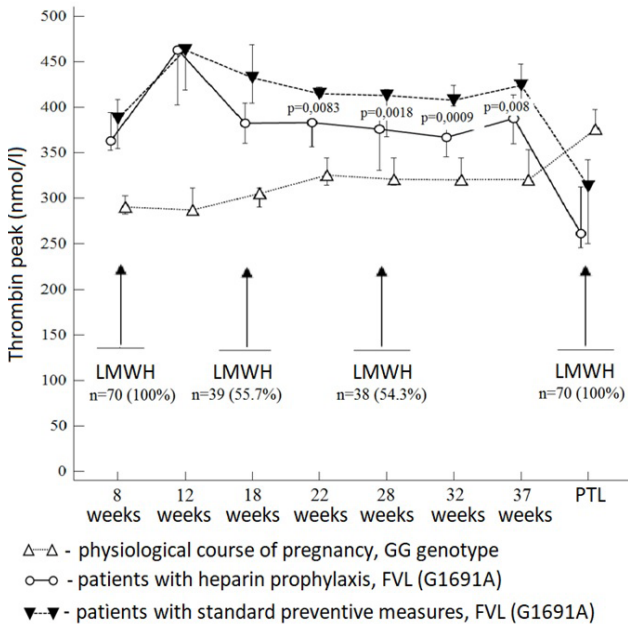

Figure 2: Dynamics of peak thrombin median in patients with FVL (1961) GG genotype and FVL (1961) GA genotype, depending on the heparin prophylaxis.

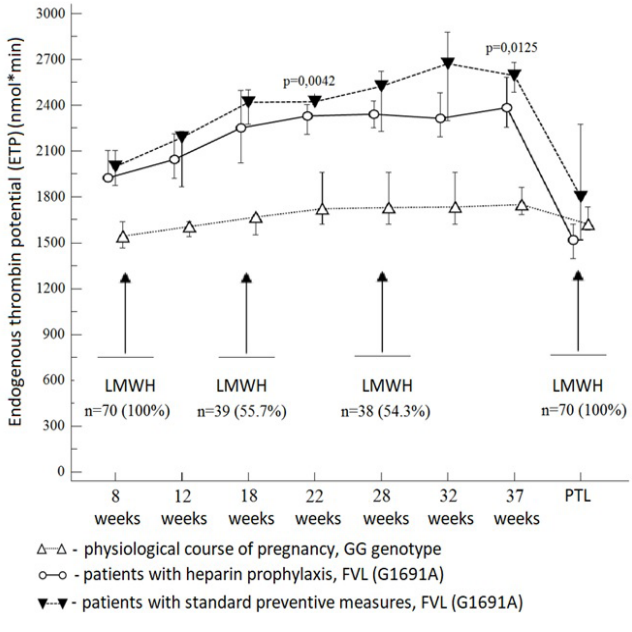

Figure 3: Dynamics of endogenous thrombin potential median in patients with FVL (1961) GG genotype and FVL (1961) GA genotype, depending on whether heparin prophylaxis was carried out or not.

Further, associations between heparin prophylaxis and the incidence of placenta-mediated complications were studied (Table 3). It was found that in the group of women who received LMWH, starting from 7-8 weeks, the number of PE cases decreased, in comparison to the standard care group, by 29.5%, FGR by 23.8%, induced PTL by 12.6% and PDONLP by 5.6%.

As a matter of end points, the values determining the degree of effectiveness of drug intervention were calculated in accordance to the accepted practice with $p < 0.05$ with respect to the number of favorable and unfavorable pregnancy outcomes with heparin prophylaxis (Table 4).

According to the presented data, in the study group there is a statistically significant ARR of PE development ($p = 0.0003$), FGR ($p = 0.0016$) and induced PTL ($p = 0.0242$). In particular, the pregnancy ended with an induced PTL in the study group in two patients (2.9% of 70), including one case of PDONLP (33 weeks) and one antenatal fetal death (32 weeks). In the control group, 11 pregnant women had induced PTL (15.5% of 71, 24-34 weeks), including 3 cases of severe PE, 3 cases of PONRP, 3 cases due to threatening intrauterine fetal asphyxia and 2 cases due to antenatal fetal death.

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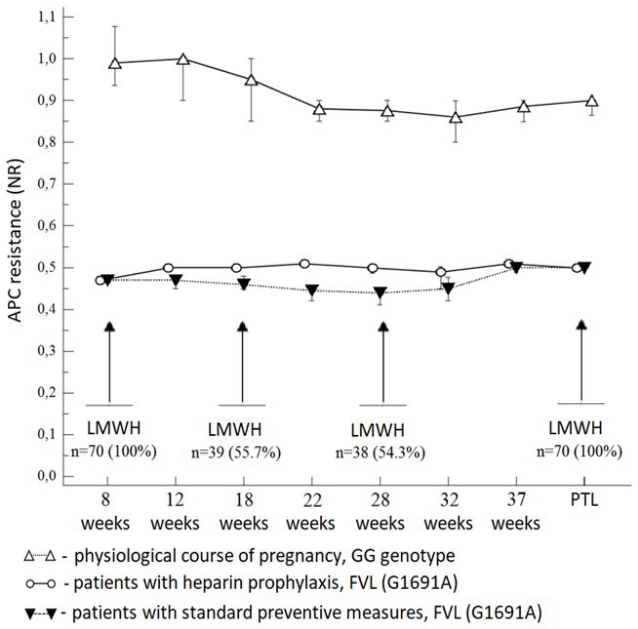

Figure 4: Dynamics of the NR median reflecting APC resistance in patients with FVL (1961) GG and GA genotypes, depending on whether heparin prophylaxis was carried out or not.

Discussion

Part 1

Previously, it was shown that the very course of pregnancy is accompanied by an increase in the haemostatic potential, including thrombin potential [44-47]. The present work, like the study of Selmeczi A et al., revealed not only a bigger increase in thrombin generation during pregnancy in FVL (1691) GA women (compared to the FVL (1691) GG genotype), but also a decrease in thrombin generation due to heparin prophylaxis [48]. In particular, suppression of thrombin generation by LMWH in comparison to the absence of heparin prophylaxis determined from 22 weeks of gestation, including median and peak thrombin was by 9.0% (p =0.0083) and ETP by 4.0% (p =0.0042).

One can also draw attention to the fact that the increase in thrombin potential is characteristic for the development of preeclampsia [49,50], and LMWH improves angiogenesis by lowering thrombin generation [51].

Part 2

After the first description of the resistance to Activated Protein C (APC resistance) in 1993 [5,52] and identifying FVL mutation responsible for this inherited, genetically conditioned resistance, numerous clinical studies identified the importance of APC resistance in the etiopathogenesis of deep vein thrombosis during pregnancy and in the puerperium. On the other hand, there are works showing that pregnancy itself has a significant effect on it [53-55]. It was shown that an increase in factor Va resistance to APC in pregnancy corresponds to an increase in the level of factor VIII and a decrease in protein S and APC inhibitor content [55,56].

Thus, it can be assumed that in women with FVL mutation, an acquired APC resistance is superimposed on its inherited form during pregnancy.

The main criterion for including patients into this study was the degree of APC resistance (NR ≤0.49), which was associated with a higher previous incidence of thrombotic and gestational complications [34]. In this study, a decrease in APC resistance was observed due to preventive doses of LMWH, which was statistically significant from 12 weeks of pregnancy. Apparently, this effect is related to the effect on the causes that determine its acquired component, which is not genetically conditioned.

Part 3

In the presented study, it was shown that the use of a prophylactic dose of LMWH for APC resistance in FVL (1961) GA women from 7-8 weeks reduces the Absolute Risk (ARR) of placenta-mediated pregnancy complications, including PE (by 29.5%), FGR (by 23.8%) and induced PTL (by 12.6%). This clinical effect is not yet fully explainable, which corresponds to the position of other authors [57].

Study Points	LMWH "-" n=70		LMWH "+" n=71			Statistical Values	
	Me	95% CI	Me	95% CI	Mann-Whitney U	Test statistic Z	p
8 weeks	0.47	0.45-0.48	0.47	0.46-0.48	2398	0.366	0.7142
12 weeks	0.46	0.44-0.48	0.5	0.47-0.51	329	3.424	0.0006
18 weeks	0.46	0.44-0.48	0.5	0.46-0.51	421	3.828	0.0001
22 weeks	0.45	0.42-0.46	0.51	0.49-0.52	173.5	4.96	<0.0001
28 weeks	0.44	0.41-0.45	0.5	0.48-0.51	111.5	4.26	<0.0001
32 weeks	0.44	0.42-0.46	0.49	0.45-0.50	162.5	2.755	0.0059
37 weeks	0.5	0.49-0.51	0.5	0.49-0.52	136	2.058	0.0396
PTL	0.5	0.49-0.51	0.52	0.47-0.53	147.5	0.424	0.6717

Table 2: NR median values depending on whether heparin prophylaxis was carried out or not at different stages of pregnancy in women with FVL (1961) GA.

Pregnancy Outcomes	LMWH "+" n=70		LMWH "-" n=71		Statistical Values		
	Total	%	Total	%	p	RR	95% CI
Total number of pregnancies	70		71				
RL before 12 weeks	0	0.0%	12	16.9%	0.0253	0.04	0.002-0.67
Total number of PE	6	8.6%	27	38.0%	0.001	0.23	0.1-0.51
Including severe PE	0	0.0%	6	8.5%	0.0802	0.08	0.04-1.35
FGR	5	7.1%	22	31.0%	0.001	0.23	0.1-0.57
Induced PTL	2	2.9%	14	15.5%	0.001	0.18	0.04-0.8
PDONLP	1	1.4%	5	7.0%	0.1405	0.2	0.02-1.69
Antenatal fetal death	1	1.4%	2	2.8%	0.5757	0.5	0.05-5.5

Table 3: Obstetric and perinatal outcomes in women with FVL (1691) GA.

Pregnancy Outcomes	LMWH "+" n=70		LMWH "-" n=71		Statistical Values			
	Total	EER	Total	CER	RRR	ARR	NNT	95% CI for NNT
Total number of pregnancies	70		71					
RL before 12 weeks	0	0.0%	12	16.9%	100%	16.9%	5.9	3.9-13.0
Total number of PE	6	8.6%	27	38.0%	77.5%	29.5%	3.4	2.35-6.12
FGR	5	7.1%	22	31.0%	76.9%	23.8%	4.2	2.8-8.7
Induced PTL	2	2.9%	11	15.5%	81.6%	12.6%	5.8	3.7-14.1

Table 4: Values reflecting the effectiveness of heparin prophylaxis in women with FVL (1691) GA and the APC resistance index ≤0.49.

In recent years, studies aimed at investigating the efficacy of heparin prophylaxis for placenta-mediated complications differ by the fact whether they consider genetic thrombophilia with a history of pregnancy complications or not. Thus, the lack of consideration of genetic predisposition to thrombosis when forming comparison groups demonstrated the lack of effectiveness of heparin prophylaxis in reducing the number of gestational complications [32,58-60].

In particular, the SPIN study (2010) aimed at studying the effectiveness of enoxaparin sodium (40 mg once daily) and aspirin (75 mg daily) in women with a history of two or more reproductive losses did not reveal any effect of the intervention. Of 147 participants receiving treatment, 32 (22%) had reproductive losses, compared to 29 (20%) of 147 women receiving only observation [OR 0.91; 95% CI 0.52-1.59] [58]. In a study by Groom et al., [OR 1.19; 95% CI 0.53-2.64] [60] the efficacy of sodium enoxaparin (40 mg daily) for preventing the recurrence of PE and FGR in women with a history of these disorders was evaluated. The study showed no effect of heparin prophylaxis on PE: 18 complications were observed in the LMWH group (25% of 72) and 17 complications were observed in the standard care group (22.1% of 77).

Stricter stratification of patients into study groups, based not only on the history of pregnancy complications, but also on its association with genetic thrombophilia, showed more interesting results [35,61]. Thus, in particular, in the study of de Vries et al. [35], including 139 women with hereditary thrombophilia, of which 82 (59.0% of 139) had FVL (1961) GA mutation, sodium dalteparin (daily at a dose of 5000 IU) in combination with acetylsalicylic acid (daily at a dose of 75-100 mg) led to Absolute Risk Reduction (ARR) of early-onset preeclampsia (up to 34 weeks) by 8.7% [95% CI (1.9-15.5) p =0.012].

Part 4

The clinical efficacy of heparin prophylaxis in women with FVL (1961) GA in this study is difficult to explain solely by the anticoagulant properties of LMWH. In recent years, other effects of LMWH have been considered, which manifest themselves in the interaction with blood vessels endothelium and extravasally.

For example, some *in vitro* studies show that LMWH enhances placental generation of the Matrix Metalloproteinase-2 (MMP-2) and the activity of Heparin-Binding Epidermal Growth Factor (HB-EGF) [62,63], which has a cytoprotective effect, regulating the proliferation, invasion and differentiation of trophoblast [64].

Moreover, according to experimental studies, it was found that LMWH is able to reduce the intensity of apoptosis of trophoblast cells during hypoxia, by increasing the secretion of HB-EGF [20,65].

McLaughlin et al., determined that LMWH has a protective effect on endothelium by stimulating the secretion of PGF from endothelial cells, including in women at high risk of preeclampsia [57].

It is believed that the aberration of trophoblast invasion leads to in sufficient placental perfusion, oxidative stress and inflammation [66,67]. Zenerino et al., described a mechanism through which

LMWH has an anti-inflammatory effect on the placental tissue. They found that LMWH can change the structure of anti-inflammatory group proteins by reducing IL-6 and TNF-α expression [68].

It can be assumed that the diversity of LMWH action during formation of the primary placenta (7-8 weeks) contributes to restoration of hemostatic balance and creation of conditions for adequate cytotrophoblast invasion.

The strengths of the present study are: Strict stratification of patients when enrolling into the study (only with FVL (1961) GA with severe APC resistance (NR ≤0.49)); the timing of heparin prophylaxis (beginning with 7-8 weeks of gestation, the period of interstitial cytotrophoblast invasion), and laboratory monitoring of LMWH effects aimed at assessing the features of thrombin generation.

The limitations to the extrapolation of the results are: Caucasian race of the patients, conducting the study in one center. In addition, the test system chosen to determine the resistance of factor Va to activated protein C cannot be generally accepted, and therefore, a specific cutoff point for NR corresponding to 0.49 may vary between test systems from other manufacturers.

Conclusion

1. Not only a more pronounced increase in thrombin generation during pregnancy in FVL (1691) GA patients (compared to the normal genotype), but also a decrease in thrombin generation due to heparin prophylaxis were found out.
2. Prophylactic doses of LMWH decrease APC resistance, which is probably related to the effect on the causes that determine its acquired component, which is not genetically determined.
3. The use of LMWH in a prophylactic dose in FVL (1961) GA patients from 7-8 weeks reduces the absolute risk of placenta-mediated pregnancy complications, including PE (by 29.5%), FGR (by 23.8%) and induced PTL (by 12.6%).

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