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Hereditary thrombophilia and low -molecular -weight heparin in women: useful determinants, including thyroid dysfunction, incorporating the management of treatment and outcomes of the entity

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SUMMARY

OBJECTIVE: Our study purposed to examine the complex relationship between low-molecular-weight heparin therapy, multiple pregnancy determinants, and adverse pregnancy outcomes during the third trimester in women with inherited thrombophilia.

METHODS: Patients were selected from a prospective cohort of 358 pregnant patients recruited between 2016 and 2018 at the Clinic for Obstetrics and Gynecology, University Clinical Centre of Serbia, Belgrade.

RESULTS: Gestational age at delivery (β=-0.081, p=0.014), resistance index of the umbilical artery (β=0.601, p=0.039), and D-dimer (β=0.245, p<0.001) between 36th and 38th weeks of gestation presented the direct predictors for adverse pregnancy outcomes. The model fit was examined using the root mean square error of approximation 0.00 (95%CI 0.00–0.18), the goodness-of-fit index was 0.998, and the adjusted goodness-of-fit index was 0.966.

CONCLUSION: There is a need for the introduction of more precise protocols for the assessment of hereditary thrombophilias and the need for the introduction of low-molecular-weight heparin.

KEYWORDS: Thrombophilia, hereditary. Pregnancy. Thyroid gland. Heparin, low-molecular-weight.

INTRODUCTION

Physiologic pregnancy is associated with increased clotting potential and decreased fibrinolysis and anticoagulant activity[1,2], as well as venous stasis in the lower extremities, which are all factors that significantly augment the likelihood of venous thromboembolism (VTE) during pregnancy[3]. The aforementioned risks seem to be accentuated[1], but the association between hereditary thrombophilias and adverse pregnancy outcomes (APO), including fetal loss, preeclampsia, fetal growth restriction, and placental abruption, is being examined among women with hereditary thrombophilias[1,2,4,5]. The disorders of hemostasis, such as hereditary thrombophilias, have been identified as health conditions that can be associated with changes in the hemodynamics of the blood flow to the fetus[6]. Poor uteroplacental blood flow can further lead to thrombi in the placenta, while hereditary thrombophilias are associated with the placental microthrombi[7-9], which leads to infarctions, decreased trophoblast invasion, hypoxia, and overall placental insufficiency associated with the APO like stillbirths and intrauterine growth restriction[7,8,10]. Adequacy of the blood flow can be examined using the Doppler ultrasound and resistance index of the umbilical artery (RiAu)[9].

There is still a lack of evidence for the utility of routine testing for hereditary thrombophilias, although numerous clinicians are ordering it in the past decades[11]. Early identification of hereditary thrombophilias and timely introduction

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of low-molecular-weight heparin (LMWH) prophylaxis may improve pregnancy outcomes[5,11,12]. As such, both aspirin and LMWH are proven to decrease the likelihood of APO among women with acquired thrombophilia, mainly antiphospholipid syndrome, but the data are less clear in cases of hereditary thrombophilias[13], and there is insufficient evidence to support the introduction of prophylactic anticoagulant treatment[3]. LMWH is the first choice anticoagulant for pregnant women as it is proven to have adequate bioavailability, predictable dose-response, and safety profile compared to unfractionated heparin[14]. Of note, the guidelines state that the introduction of anticoagulant therapy in pregnant women with hereditary thrombophilias should be based on individual risk assessment and focused on the personal and family history of VTE and risk factors for VTE, such as obesity, prolonged immobility, or cesarean delivery[1,15], relatively frequent in the Balkan region[5].

This study purposed to examine the complex relationship between LMWH therapy, multiple pregnancy determinants, and APO during the third trimester with inherited thrombophilia.

METHODS

In this study, patients had been incorporated from a prospective cohort of 358 pregnant recruited between 2016 and 2018 at the Clinic for Obstetrics and Gynecology, University Clinical Centre of Serbia, Belgrade, Serbia[12]. Briefly, the study endorsed all the referred women with inherited thrombophilia between 11 and 15 weeks of gestation and followed up to the delivery. The examined parameters were laboratory parameters and Doppler flows of the umbilical artery at 28th to 30th, 32nd to 34th, and 36th to 38th gestational weeks (gw), use of LMWH prophylaxis, and obstetric and perinatal outcomes. For this study, we incorporated the cases with the complete data on values of the RiAu between 36th and 38th weeks of gestation and values of D-dimer between 36th and 38th weeks of gestation.

The exclusion criteria were as follows:

(1) age >40 years;
(2) ovarian cell donation;
(3) concurrent hereditary and acquired thrombophilia;
(4) congenital anomalies of the uterus;
(5) multiple pregnancies;
(6) previous gynecological surgery;
(7) presence of perinatal infections (TORCH);
(8) type 1 diabetes, preexisting arterial hypertension;
(9) previous kidney transplantation;
(10) extreme obesity (BMI >40 kg/m^2);
(11) use of LMWH due to any comorbid condition other than hereditary thrombophilia;
(12) abnormal findings in the first-trimester prenatal screening tests, fetal anomalies, central placenta previa, and pathological degree of placental nidation (suspect for placenta acreta, increate, or percreta); and
(13) therapeutic use of LMWH during pregnancy.

The data for the study were drawn from the patient records in the hospital database, including age, comorbid conditions (pulmonary embolism, insulin resistance, thyroid dysfunction), adverse health outcomes in the family history (arterial hypertension, HA; deep venous thrombosis, DVT; myocardial infarction, MI; cerebrovascular insult, CVI; pulmonary embolism, PULME; thyroid dysfunction, THR) if thrombophilia was recognized prior to the current pregnancy, previous APO, type of mutation responsible for thrombophilia (plasminogen-activator inhibitor, PAI; factor V Leiden; MTHFR mutation; prothrombin G20210A; protein S deficiency; factors VII, IX, and XI; or anti-thrombin-related mutation), mode of delivery, APO in the current pregnancy (in our study, we recorded pregnancy losses in the third trimester—intrauterine fetal death—preterm birth, fetal growth restriction), values of resistance index of umbilical artery (RiAu) between 36th and 38th weeks of gestation, and values of D-dimer between 36th and 38th weeks of gestation, the LMWH therapy in the current pregnancy, gestational age at delivery, and fetal sex. The characteristics of the participants from the original cohort are presented elsewhere[12]. From the cohort of 358 pregnant patients, 203 had complete data on values of the RiAu between 36th and 38th weeks of gestation and values of D-dimer between 36th and 38th weeks of gestation and were selected for the analysis. These cases were classified into two groups according to the presence of APO in the current pregnancy: group with APO (33 cases, 16.3%) and group without APO (170 cases, 83.7%).

The statistical analyses were conducted using the methods of descriptive and analytical statistics. To this end, the means, standard deviations, skewness, and kurtosis were calculated for numerical data, and categorical variables were presented by absolute numbers with percentages. The differences between the groups with APO and without APO were analyzed using the chi-square (χ^2) test for categorical variables and the Student's t-test for numerical variables. The path analysis was conducted to examine the relationship between LMWH therapy, previous APO, gestational age at delivery, RiAu between 36th and 38th weeks of gestation, D-dimer value between 36th and 38th weeks of gestation, and APO. Multiple measures were used to assess the adequacy of model fit to the data: the chi-square test and the fit indices such as the comparative fit index (CFI), the normed

fit index (NFI), the adjusted goodness-of-fit index (AGFI), and the root mean square error of approximation (RMSEA). The model consistency was evaluated by the chi-square test, which indicates, when nonsignificant, that the data are consistent. The acceptable model fitting values for fit indices were defined as follows: CFI ≥0.95, NFI≥0.95, AGFI ≥0.95, and RMSEA <0.05. In all the analyses, the significance level was set at 0.05, and the statistical analyses were performed using the Amos 21 (IBM SPSS Inc., Chicago, IL, USA) and IBM SPSS Statistics 25 software.

RESULTS

The groups with and without the APO in the current pregnancy differed significantly in the frequency of the previous APO (p=0.031). The patient history characteristics of the current study sample are presented in Table 1. The women with APO in current pregnancy had significantly higher RiAu between 36th and 38th weeks of gestation (0.69±0.08 vs. 0.57±0.08, p<0.001), significantly higher D-dimer between 36th and 38th weeks of gestation (2.74±1.06 vs. 0.68±0.48, p<0.001), and significantly higher frequency of gestational age at delivery between 36th and 37th weeks (42.4 vs. 2.9%, p<0.001) compared to the women without APO in the current pregnancy. A sum of 27 (13.3%) women had been detected as possessing thyroid dysfunction, and the cases with APO in the current pregnancy had no significance compared to the ones without APO in the current pregnancy. The characteristics of the current pregnancy of patients in both groups are presented in Table 2.

We conducted a path analysis with APO as the target variable. The absolute fit index (χ^2=0.983, df=1, p=0.321) demonstrated a good fit to the data. The values for fit indices NFI (0.998), AGFI (0.966), and CFI (1.000) were above the cutoff value of ≥0.95. The RMSEA value of 0.000 (0.000–0.185) was below the suggested value of ≤0.05. Of note, Figure 1 presents the results from the path analysis, and the path analysis exhibited that the gestational age at delivery (β=-0.081, p=0.014),

Table 1. Characteristics of patient history.

Variables	Total n (%)	APO in current pregnancy n (%)	No APO in current pregnancy n (%)	p-value
Maternal age, years, mean±SD	31.57±5.74	33.68±4.29	33.67±3.96	0.993
Comorbidities, conditions, or previous adverse health events				
Pulmonary embolism	1 (0.5)	0 (0)	1 (0.6)	0.659
Insulin resistance	22 (10.8)	4 (12.1)	18 (10.6)	0.795
Thyroid dysfunction	27 (13.3)	4 (12.1)	23 (13.5)	0.827
Adverse health outcomes in family history, n (%)				
HA	32 (15.8)	2 (6.1)	30 (17.6)	0.095
DVT	4 (2.0)	0 (0)	4 (2.4)	0.373
MI	5 (2.5)	1 (3.0)	4 (2.4)	0.818
CVI	5 (2.5)	1 (3.0)	4 (2.4)	0.818
PULME	2 (1.0)	0 (0)	2 (1.2)	0.531
THR	5 (2.5)	0 (0)	5 (2.9)	0.318
Type of inherited thrombophilia				
PAI-1	27 (23.5)	4 (25.0)	23 (23.2)	
MTHFR	12 (10.4)	1 (6.3)	11 (11.1)	
FVL	9 (7.8)	1 (6.3)	8 (8.1)	
PT	7 (6.1)	0 (0)	7 (7.1)	
Other	4 (3.5)	1 (6.3)	3 (3.0)	
Combined thrombophilia	53 (46.1)	7 (43.8)	46 (46.5)	0.211
Previous APO (any)				
Yes	90 (44.3)	9 (27.3)	81 (47.6)	
No	113 (55.7)	24 (72.7)	89 (52.4)	0.031

RiAu (β=0.601, p=0.039), and D-dimer (β=0.245, p<0.001) between 36th and 38th gw presented the main direct predictors for APO. The important indirect effects on APO were recognized in LMWH therapy via the RiAu between 36th and 38th gw and for previous APO via the D-dimer between 36th and 38th gw.

Table 2. Characteristics of the current pregnancy.

Variables	Total n (%)	APO in current pregnancy n (%)	No APO in current pregnancy n (%)	p-value
Ri 36-38 gw, mean±SD	0.59±0.09	0.69±0.08	0.57±0.08	**<0.001**
D-dimer 36–38 gw, mean±SD	1.02±0.97	2.74±1.06	0.68±0.48	**<0.001**
Delivery				
Vaginal	39 (19.2)	8 (24.2)	31 (18.2)	
Cesarean section	164 (80.8)	25 (75.8)	139 (81.8)	0.423
Gestational age at delivery				
38–39 gw	184 (90.6)	19 (57.6)	165 (97.1)	
36–37 gw	19 (9.4)	14 (42.4)	5 (2.9)	**<0.001**
Fetal sex				
Male	111 (54.7)	17 (51.5)	94 (55.3)	
Female	92 (45.3)	16 (48.5)	76 (44.7)	0.690
LMWH therapy				
Yes	128 (63.1)	17 (51.5)	111 (65.3)	
No	75 (36.9)	16 (48.5)	59 (34.7)	0.133

Bold values indicate statistical significance at the p<0.05 level.

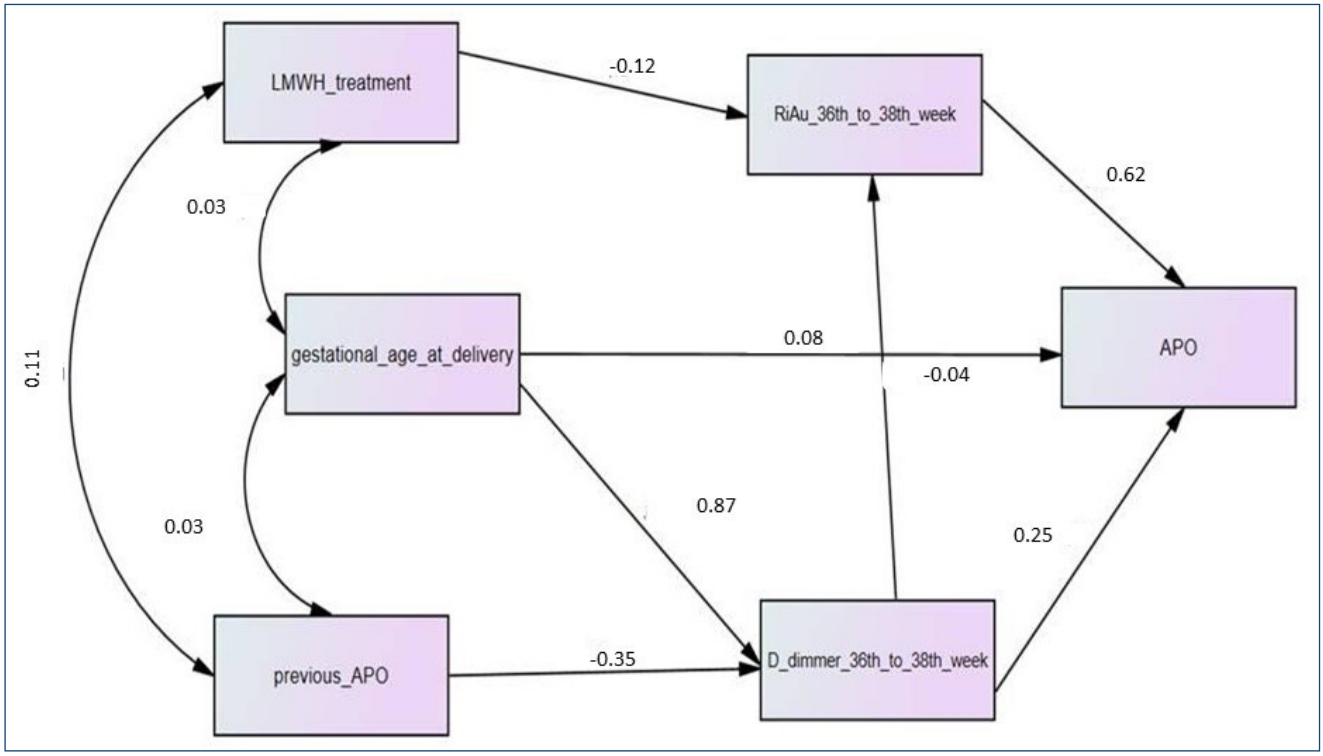

Figure 1. A path model presenting the complex relationship between low-molecular-weight heparin therapy, multiple pregnancy determinants, and adverse pregnancy outcomes during the third trimester in cases with inherited thrombophilia.

DISCUSSION

Some authors suggested that all pregnancies with hereditary thrombophilias should be considered high-risk pregnancies with a high likelihood of APO[16]. However, contradictions remain in the recommendations on their follow-up and prophylactic administration of LMWH, as the routine administration of LMWH is still not recommended[1,3]. The LMWH therapy was, in this study, significantly negatively associated with the RiAu between 36th and 38th gw. The lower gestational age on delivery, higher D-dimer values, and higher RiAu values were associated with APO, and the LMWH therapy had an indirect effect on APO via RiAu between 36th and 38th gw. These findings indicate that previous APO should also be included in the evaluation of the necessity for inclusion of LMWH therapy in order to achieve the attenuation of the occurrence of APO in the current pregnancy[3,12].

There is a need for further randomized controlled trials, as the TIPPS and FRUIT trials, large randomized controlled trials on the use of LMWH, did not show significant benefits. Additionally, some data show that the pathogenic process might originate in the first trimester and that LMWH treatment can have benefits during implantation and placental development. This is why it may be important to evaluate the timing of the initiation of LMWH treatment, especially its introduction in the first trimester, which recommendation is also in accordance with our results as the participants were recruited in the late first or early in the second trimester[17].

It is known that reproductive functions are affected by some conditions, the thyroid hormones, L-thyroxine (3,5,3',5'-tetraiodothyronine, T4), and L-triiodothyronine (3,5,3'-triiodothyronine, T3). These hormones are also known as vital parameters for the normal reproductive function of humans and animals employing regulation of the ovarian, uterine, and placental tissues and metabolism in thyroidology[18]. However, in this study, the cases with APO in the current pregnancy have not revealed any significance compared to the ones without APO in the current pregnancy in terms of thyroid dysfunction.

The RiAu was associated with the LMWH treatment and with APO in the current pregnancy in our study. The higher RiAu was previously shown to be associated with low birth weight and lower fetal weight gain during the third trimester[19]. Of note, the pathophysiology of the low birth weight of the newborns of women with thrombophilias is based on an association of hereditary thrombophilias with placental infarction, abnormal trophoblast invasion, and chronic hypoxia, leading to increase in uterine artery resistance[3]. Attenuation in RiAu in the third trimester may enable the higher fetal growth potential, the higher potential for the adequate duration of the gestational period[19], and decrease the likelihood for APO, as we also found a negative association between the gestational age at birth and APO. In addition, augmented D-dimer values were recognized in the second and third trimesters in most pregnant women[19], but the higher D-dimer values with higher RiAu and a higher likelihood for APO were recognized in this study.

Limitations

The main limitation of our study is in the observational design as our participants were not randomized to the groups examined, and there could be bias in the classification of the participants to the examined groups. However, there were no significant differences in the characteristics of pregnant women from both groups in the age, BMI, and frequencies of most different thrombophilia types.

CONCLUSION

The lower gestational age on delivery, higher D-dimer values, and higher RiAu values during the third trimester were associated with APO. As adequate blood flow allows adequate fetal development through the transition from a high to a low resistive blood flow, and clotting disorders can be considered as the factor associated with the interruption of this process, the adequate values of the RiAu throughout the pregnancy are important for the prevention of the APO. The LMWH therapy had an indirect effect on APO via RiAu, yielding further research on the importance of its timely introduction among pregnant women with hereditary thrombophilias, which can allow for the prevention of APO, their consequences for pregnant women later life, and the consequences of a suboptimal uterine environment for the child's development and future life. *Neque ignorare medicum oportet quæ sit ægri natura.*

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AUTHORS' CONTRIBUTIONS

SD: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. **MP:** Investigation, Project administration, Resources, Validation, Visualization, Writing – original draft. **DS:** Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. **DAD:** Investigation, Methodology, Software, Validation, Visualization, Writing

– review & editing. **IS:** Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing. **ECAV:** Investigation, Methodology, Validation, Visualization, Writing – review & editing. **TS:** Data curation, Formal Analysis, Investigation, Project administration, Resources, Validation, Visualization, Writing – original draft. **MM:** Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft. **JT:** Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft. **MG:** Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft.

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